ORIGINAL

Before the
U.S. Food and Drug Administration
Rockville, MD

In the Matter Of:	)	
Request for Comment on First Amendment Issues	)	**Docket No. 02N-0209**

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COMMENTS OF PFIZER INC

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EXECUTIVE SUMMARY:

COMMENTS OF PFIZER INC.

in Response to
FDA Request for Comments on First Amendment Issues

Pfizer endorses FDA's decision to consider how the First Amendment affects the agency's approach to regulating pharmaceutical manufacturer speech about prescription drugs. FDA's request for comments ("the Request") is timely in several respects. As the Request notes, recent court decisions indicate that FDA must be cautious in seeking to restrict or manage the flow of truthful and useful information that manufacturers add to today's dynamic interchange of data concerning drug products. In addition, the Request provides FDA an opportunity to assess the legal issues in light of the growing body of favorable empirical evidence concerning direct-to-consumer ("DTC") advertising. The facts amassed since 1997, when the agency liberalized its DTC constraints, show that these promotional communications have enhanced the delivery of health care in the United States. Moreover, the Request allows FDA scope to evaluate relevant First Amendment principles and empirical experience against the background of broader developments in U.S. health care, including the growing trend toward more sophisticated dialogue between patients and their physicians[1] about drug treatment options as well as expanding public debate – much augmented and transformed by the Internet as a communications medium used by scientists and others – about the benefits and risks of prescription drug therapies.

Pfizer is submitting extensive comments on the First Amendment issues raised in the Request. These comments are designed to provide FDA with a thorough, rigorous legal analysis

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1 Unless the context otherwise indicates, Pfizer in its comments and this summary uses the terms "physicians" and "doctors" to refer to all health-care professionals authorized to prescribe pharmaceuticals regulated under 21 U.S.C. § 353(b).

of the agency's authority to continue its regulation of drug manufacturer speech at various stages of drug development and marketing. Through its efforts, Pfizer hopes to assist FDA to better comprehend the constitutional limits of the agency's power to evaluate, ban, pre-clear, restrict, or mandate speech. This understanding should equip FDA to prepare to successfully defend its actions against future First Amendment challenges. In certain cases, this preparation simply requires a sophisticated application of the relevant law, while in other instances the agency should modify its rules and policies to better conform to constitutional requirements.

Pfizer does not intend, however, to suggest that any legal analysis necessarily resolves all policy issues, or establishes a complete set of "best practices" with respect to pharmaceutical industry communications about prescription drugs, or requires any manufacturer to depart from existing FDA policies. To the contrary, the company's comments also point out that FDA's ability to provide public health leadership is not unduly hampered by the Constitution. In those areas where the First Amendment constrains the agency from imposing sweeping, categorical speech rules, the agency remains free to encourage the industry voluntarily to shape its messages in ways that the government considers to best serve the public health – by providing various compliance incentives, including "safe harbors" against later enforcement or liability actions.

FDA's Core Missions Are Consistent with the First Amendment

At the outset of its detailed analysis, Pfizer makes plain that it supports FDA on several key points. Respect for First Amendment values does not, as some might argue, require adoption of an extremist position that no FDA speech restraint is viable. Rather, regulatory review of certain information flows is essential to protection of the public health. It is entirely appropriate, for example, for the agency to determine its jurisdiction over products on the basis of the claims their manufacturers make about them. FDA also properly directs detailed regulatory oversight to

the dosage, safety, and other use information accompanying a drug. Pfizer recognizes and supports two core missions assigned to the agency: (1) ensuring that the prescription drugs made available to the American public are safe and effective; and (2) requiring that the promotion of those drugs be truthful and non-misleading. Pfizer's analysis suggests how public health and First Amendment interests can be harmonized to create a legally sustainable regulatory regime that better serves U.S. consumers and medical professionals.

As a major developer of new prescription drugs and the scientific and clinical information related to them, Pfizer has a critical interest in informing physicians and patients about its innovations. Providing information about its products accelerates the beneficial use of new Pfizer prescription drugs, thereby improving consumer health more quickly than would otherwise occur. The company also is keenly interested in responding to those who exercise their own First Amendment privileges to critique Pfizer products. Further, Pfizer believes it is essential to maintain a two-way flow of information with the medical community about the company's products because such communications help both the company and physicians in managing drug risks and optimizing drug usage.

Old, paternalistic traditions in health care administration explain why FDA might once have believed that onerous regulation of manufacturer speech about pharmaceuticals was necessary to protect the public health and to preserve the central role of physicians in drug therapy. But studies of the impact of DTC advertising – some conducted by FDA itself – now conclude that a vibrant flow of information about prescription drugs to consumers has great value. Surveys reveal that well over 60% of consumers agree that DTC ads alert them to symptoms requiring physician attention, better enable them to inquire about treatment options, and enhance their ability to engage in informed discussion with their doctors about drug benefits

and risks.2 According to the data, DTC ads prompted more than 50% of consumers to seek additional information about conditions and treatments.3 As a consequence, the advertisements led an estimated 25 million consumers to ask their doctors about particular conditions for the very first time.4 Eighty percent of consumers who raised questions based on a DTC ad reported that their physicians were "very willing" to respond constructively.5 This finding is consistent with physician surveys, in which more than 61% of those responding report that DTC advertising enhances their interactions with patients.6 In an era when financial constraints limit the time for face-to-face dialogue between physicians and consumers, it is not surprising that both parties appreciate the educational assistance provided by the information in DTC ads. Given these facts, Pfizer believes that FDA should approach its First Amendment review with an appreciation for the health-care benefits generated by greater information flows concerning prescription drugs.

The Once-Separate Development of FDA Law and First Amendment Law Has Converged

In its comments, Pfizer begins its substantive legal analysis by reviewing the historic roots and evolution of FDA's role in the prescription drug marketplace. As noted above, FDA has two related, valuable missions that reflect somewhat different government interests. First, since 1962, FDA has ensured that prescription drugs are not distributed to the public unless they

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2 Scott-Levin, *DTC Audit*, 2001; Prevention, *Annual DTC Study*, 2001.

3 Office of Medical Policy, Division of Drug Marketing, Advertising, and Communications, Attitudes and Behaviors Associated with Direct-to-Consumer (DTC) Promotion of Prescription Drugs – Main Survey Results (1999), available at http://www.fda.gov/cder/ddmac/dtcindex.htm.

4 Prevention, *Annual DTC Study*, 2001.

5 *Id.*; *see also* Kathryn J. Aikin, Division of Drug Marketing, Advertising & Communications, FDA, *Direct-to-Consumer Advertising of Prescription Drugs: Preliminary Patient Survey Results*, at 31 (Apr. 18, 2002) (93% of patients who had a conversation with their doctor about a prescription drug said that their doctor welcomed the question; 83% said the doctor reacted as if the question were a normal part of the visit).

6 Market Measures Interactive, *DTC Cholesterol & Mood/Anxiety Disorders: Doctor Dialogues* (July 2001) (survey based on physician reports on over 400 office visits where patients initiated a discussion about a prescription drug).

are scientifically proven to be both safe and effective for use. This FDA role as a "gatekeeper" to the marketplace is a modern offshoot of the government's centuries-long interest in validating the qualifications of those offering health-care services to the public. Second, FDA is responsible for preventing those who sell prescription drugs from disseminating false or misleading information about the products. This mission casts FDA in the role of supervising promotional messages – much as the Federal Trade Commission does with respect to advertising in other industries – and arises from the traditional government interest in ensuring the integrity of the commercial marketplace. FDA must carefully delineate the role it is serving at any particular point in its regulatory process in order to determine how the First Amendment affects the agency's authority over the flow of prescription drug information.

Pfizer's comments next analyze the evolution of free speech doctrine in the courts. The analysis traces the growing recognition, culminating in *Thompson v. Western States*, 122 S. Ct. 1497 (2002), that FDA's comprehensive regulatory powers are subject to First Amendment scrutiny. The level of scrutiny that a court would train on a challenged FDA action will vary by context. Certain cases are likely to trigger the highest degree of constitutional scrutiny, such as those instances when FDA attempts to bar manufacturers from disseminating valid scientific information to promote professional dialogue with physicians and health-care organizations or when the agency suppresses a manufacturer's response to public concerns raised about the safety or efficacy of its products. In these instances, FDA's actions will be upheld only in very rare circumstances. Reviewing courts will give FDA somewhat greater latitude in controlling manufacturer efforts to promote product sales – so-called "commercial speech" – but the agency still must justify any restrictions by showing that they directly advance a substantial government interest and are narrowly tailored to achieve that result with minimal impediments on valuable

information flows. FDA also has power to ban commercial speech found to be false or misleading so long as it has a factually and procedurally defensible basis for that finding. Yet even in these cases, the courts will require the agency to consider less speech-restrictive alternatives, such as mandatory disclosures that would cure potentially misleading messages, in lieu of outright suppression. Court scrutiny will be most deferential in cases where FDA's restrictions are not directly aimed at the information flow but instead are simply incidental to the agency's interest in regulating conduct. Thus, for example, FDA adoption of a common labeling format intended to enhance the safe use of prescription drugs generally will be upheld so long as the rules are not unreasonably broad or burdensome.

Application of First Amendment Scrutiny to FDA Regulations Produces Mixed Results

Pfizer then applies this analytical framework to FDA's extensive regulation of manufacturer speech about their drug products. That analysis demonstrates that much of the agency's regime – particularly those elements most central to FDA's gatekeeper role – is essential to the public health and within constitutional boundaries. Certain restraints on information flows, however, cannot withstand First Amendment scrutiny. Where FDA seeks to restrain the flow of information about lawfully marketed products, its attempts to wield plenary power are vulnerable to legal challenge.

At the outset of the regulatory process, FDA's performance of its gatekeeper function over the entry of safe and effective drugs into the marketplace requires that the agency be able to determine whether a substance is being offered as a "drug" and therefore subject to prior regulatory approval. In making this determination, the agency properly focuses on the claims made by manufacturers about a substance. Although this examination attaches regulatory consequences to manufacturer speech, any consequential restraint on communication is

into the commercial speech category, where FDA has greater scope to act, but a number of the agency's existing rules and policies appear to fall afoul of the Supreme Court's existing legal standards for permissible commercial speech regulation. In addition, FDA, for largely historical reasons, has treated many manufacturer communications as "labeling" when the courts most likely would regard them as protected commercial speech; accordingly, the agency's regulations in this area likely would receive less deference from a reviewing court than would FDA's controls over the operative labeling.

As a threshold issue, FDA, as a supervisor of the accuracy of promotional messages about prescription drugs, must first determine what message is being conveyed to the audience and then compare that message to what the agency deems to be scientific truth. Yet FDA has no agency expertise in determining "take away" or perceived messages on the part of either professional or non-professional audiences; no designated administrative hearing procedures for allowing either FDA's evaluation of the message or the agency's perception of truth to be tested; and no system for reporting FDA determinations so that the public – including regulated speakers – can review and interpret agency precedent on whether particular messages are false or misleading. Pfizer recommends that FDA cure these deficiencies by (1) extending its existing informal hearing procedures to permit neutral resolution of disputes over allegedly false and misleading ads and (2) making the results of those determinations publicly available to provide for industry guidance and public oversight.

These procedural problems highlight a constitutionally significant flaw in FDA's current approach to supervising promotional communications: rather than employ transparent and neutral evaluation procedures that allow for case-specific reviews that best accommodate First Amendment values, the agency has relied on overbroad, categorical speech restraints that are

highly restrictive and administered – at least at times – in a highly opaque manner. Pfizer's detailed analysis concludes that, absent significant liberalization, many of FDA's categorical interventions would not withstand First Amendment scrutiny.

One illustration of this issue is FDA's controls over the information flow concerning drugs undergoing agency review. FDA effectively seeks to ban all manufacturer commercial speech about drugs still in the approval pipeline other than disclosure required by the SEC, presumably because the agency has not yet determined what claims may properly be made for those drugs. This regulatory stance ignores the fact that such speech suppression does little to protect the public health from injury because the substances themselves are not yet available in the marketplace. This approach also is at odds with the general First Amendment teaching that the burden of establishing falsity lies with the government. Pfizer believes that it would be appropriate for FDA to acknowledge greater freedom for constitutionally protected public discussion of drugs under FDA review while also protecting the public health by requiring that manufacturer messages be accompanied by clear disclaimers concerning a drug's approval status, including the possibility that approval may not ultimately be secured. FDA also could lawfully reserve the right to mandate corrective action to remedy any post-approval spillover of false or excessive pre-approval claims.

As noted above, FDA categorizes most manufacturer promotional messages to doctors and other prescribing professionals as "labeling" and subjects them to extensive fair balance requirements. In imposing such overbroad mandates, the agency fails to fully recognize the reality and value of promotional speech, which serves to enhance physician consideration of treatment options and highlight scientifically established drug benefits. Indeed, FDA does not even permit manufacturers to respond to challenges to the safety or efficacy of their products

from unregulated third parties unless the regulated entity shoulders the additional burden of "balanced" disclosures that substantially dilute the effectiveness of manufacturer messages in public debate.

Pfizer believes that truthful, non-misleading promotion is essential in a private enterprise health care system. Accordingly, FDA, consistent with the Supreme Court's reasoning in *Kordel v. United States*, 335 U.S. 345 (1948), should distinguish between operative labeling and promotional communications. The agency can and should closely regulate the former as the central working tools upon which physicians rely in administering prescription drugs. FDA should hone its regulation of promotional communications, however, to focus on preventing false and misleading messages. In this regard, Pfizer offers several recommendations that will better serve public health goals while also simplifying speech requirements imposed on manufacturers. FDA should replace its detailed disclosure mandates for truthful non-misleading professional advertising with a simple statement that the material is promotional and should not be considered a substitute for the operative labeling. The agency also should liberalize its rules regarding reasonable comparisons between drug products and revoke its requirements concerning prominent placement of generic names of branded products. In addition, Pfizer urges FDA to recognize a manufacturer "right of response" when third parties make particular drugs the subject of public controversy.

Pfizer's analysis of DTC advertising regulation closely tracks the company's analysis of professional promotion rules and policies. In fact, consumer promotion creates very limited health-care risk: because a consumer must secure a prescription from a physician, that professional intervention is a safeguard against layperson misunderstanding of a DTC ad's message – and therefore the kind of "less speech-restrictive alternative" favored under First

Amendment precedent. Accordingly, Pfizer believes that a more focused DTC disclaimer highlighting the need for physician consultation and professional diagnosis would better serve First Amendment and public health goals than the current set of detailed mandatory disclosures, which can be confusing and unnecessarily raise the cost and dilute the promotional benefit of consumer advertising. Moreover, from the perspective of fostering greater health literacy among consumers, there is no evidence to show that the current disclosure mandates actually serve to educate non-professionals in any relevant sense.

With respect to FDA's approach to manufacturer circulation of information relating to unapproved ("off label") uses of approved drugs, Pfizer's analysis recognizes that a tension exists between FDA's legitimate interest in ensuring that all uses claimed by a manufacturer are evaluated for safety and efficacy and Congress' determination that physicians must be able to prescribe approved drugs as they see fit. The fact that doctors may lawfully prescribe drugs for off-label uses gives substantial First Amendment value to valid information concerning such uses. The agency has been overbroad in suppressing manufacturer circulation of this valuable information, often generated and initially published by third parties, by attributing promotional intent to *bona fide* informational efforts. Pfizer recommends that off-label information circulated with a clear disclaimer of FDA approval and without express manufacturer endorsement be deemed non-promotional, at least absent evidence of an evasive endorsement campaign.

* * *

In sum, Pfizer believes that FDA should adjust its regulatory approach to the objective behind each of its restraints on manufacturer speech. The agency should continue closely to regulate operative labeling, which has an indispensable role in ensuring safe and effective drug use. With respect to promotional communications, however, FDA should take a targeted approach that focuses on demonstrably false or misleading materials – and thereby support the

contributions of such communications in alerting consumers and physicians to potentially valuable new treatments. This sensible, two-tier regulatory regime will further the agency's mission as the scientific gatekeeper for drugs while respecting manufacturers' First Amendment right to engage in truthful and non-misleading promotional communications.

Pfizer awaits the comments of other interested parties and looks forward to the reply process.

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COMMENTS OF PFIZER INC

I. INTRODUCTION

Pfizer Inc ("Pfizer") hereby responds to FDA's May 16, 2002 Request for Comments on First Amendment Issues ("Request").[7] Pfizer believes that a comprehensive review of FDA's role in regulating the dissemination of information relating to prescription drugs is both timely and appropriate. FDA has perceived correctly that a number of critical developments in First Amendment cases, the information marketplace, and the role of individuals in health-care decisions have arisen since the years when FDA developed most of the regulations and guidances relevant here. These recent trends warrant the comprehensive reevaluation FDA is initiating.

Pfizer believes that the purpose of that reevaluation, as detailed below, should be to ensure that FDA's information management regime truly serves the public health interests that are at the core of the agency's mission without compromising the protected rights of

7 *See* Request for Comment on First Amendment Issues, Docket No. 02N-0209, 67 Fed. Reg. 34942 (May 16, 2002) ("Request").

manufacturers, physicians,[8] and patients to exchange useful and reliable information regarding the safe and effective use of regulated articles. Pfizer endorses FDA's public health and consumer protection mission; the history underlying the passage of the 1906, 1938, and 1962 Acts amply demonstrates that pre-marketing approval of new drugs and federal government supervision of drug safety and efficacy is required to discipline those who would prey upon the public with useless, deceptive, or unsafe health-care products. Pfizer also recognizes that FDA's public health mission requires the agency to monitor, regulate, and act upon certain "information flows" relating to regulated products and that a one-dimensional interpretation of the First Amendment could hobble the agency's essential regulatory role. Pfizer is confident, however, that public health and First Amendment interests can be harmonized to create an enhanced, legally sustainable FDA regime.

A. PFIZER'S INTEREST

Pfizer was founded in 1849 and today ranks as the leading research-based pharmaceutical company in the world, making innovative, safe, and effective products available to advance human and animal health in more than 150 countries. Without taking account of the pending Pharmacia merger, Pfizer has an approximately $5.3 billion research budget for the year 2002. The company employs thousands of scientists, including licensed physicians and veterinarians, with advanced degrees in all basic scientific areas and such relevant specialties as pharmacology and biochemistry. The company also maintains scientific links with more than 250 partners in academia and industry. Pfizer generates new and useful chemical and biological products, as well as a vast body of constantly evolving knowledge about those products that emerges through clinical evaluation and consumer use.

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[8] Unless the context otherwise indicates, "physicians" and "doctors" refer to all health-care professionals authorized to prescribe pharmaceuticals regulated under 21 U.S.C. § 353(b).

Pfizer believes that it has both a right and responsibility to disseminate truthful and nondeceptive information relating to its products to the health-care community and the consumer population that it serves. This exchange of information makes doctors and patients more quickly aware of valuable new drug treatments in which the company has invested massive research and development ("R&D") resources. By facilitating the dissemination of health-care condition and product information that stimulates awareness and which prescribers and consumers might otherwise find time-consuming and costly to acquire, Pfizer promotes the public health. The company also believes that this information dissemination speeds recognition of potential new uses for existing products and assists pharmaceutical companies in managing the risks inherent in all drugs that come to light over time.

For these reasons, Pfizer believes that the accelerating development of a responsible marketplace of ideas with respect to health-care products and services is beneficial as well as consistent with First Amendment values. Pfizer does not stand with those who believe in a paternalistic approach in which the husbanding of information concentrates knowledge and power in professional and governmental hands. Neither does Pfizer take the part of those who would obliterate all distinction between learned intermediaries and even the best-informed consumers. Rather, Pfizer supports an environment of truly informed consent in which the free flow of information generates a meaningful dialogue between manufacturers, prescribers, and consumers, permitting consumers to appreciate and enhance the decisions that, apart from the use of over-the counter ("OTC") drugs, ultimately must be made by licensed professionals.

B. PUBLIC POLICY CONSIDERATIONS IN PRESCRIPTION DRUG ADVERTISING

FDA's Request comes at a time of vigorous public policy debate over the role and value of advertising, particularly direct-to-consumer ("DTC") advertising, in the marketing of

prescription drugs. Pfizer understands that the Request did not specifically call for a discussion of this public policy issue. Nevertheless, in balancing the benefits and burdens of any government-imposed restriction on the flow of information relating to prescription drugs, it is important to understand how such information flows affect the public health. Thus, as background to Pfizer's detailed exploration of the constitutional issues raised by the Request, Pfizer first briefly discusses the value of prescription drug advertising, including DTC ads, in a market where purchasing decisions ultimately and properly are controlled by licensed prescribers ("learned intermediaries") rather than consumers.

1. The Empirically Validated Value of Advertising

A vast array of research and economic analysis strongly suggests that advertising – *i.e.*, the provision of information by a seller to an intended audience to induce sales[9] – has significant value. Nobel laureate George Stigler, who extensively studied the economics of information, is one of the most prominent defenders of advertising. Stigler argues that advertising increases economic performance by reducing the cost of obtaining information[10] and lauds advertising as "an immensely powerful instrument for the elimination of ignorance."[11] Advertising also is generally thought to stimulate competition and reduce prices, which has led the Federal Trade Commission to aggressively oppose restrictions on advertising in a variety of areas, including legal services, eyeglasses, and retail drug pricing.[12]

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[9] *See, e.g.*, Howard Beales & Timothy J. Muris, *State and Federal Regulation of National Advertising* 2 (1993) (noting the FTC's current belief that "advertising appropriately constrained, is a powerful tool for reducing consumer ignorance).

[10] *See id.* at 7 (*citing* George J. Stigler, *The Economics of Information*, 64 J. Pol. Econ. at 213 (1961)).

[11] *See id.* (*citing* Stigler, 64 J. Pol. Econ. at 220).

[12] *See* FTC Press Release, *FTC Staff Cautions Bar Association Against Undue Restrictions on Lawyer Ads* (June 29, 1994), *available at* http:www.ftc.gov/opa/predawn/F95/lawyerads.htm ("'[S]ome rules addressed to particular risks of deception may be too broad; by preventing the communication of truthful and nondeceptive information that

Prescription drug advertising carries particular benefits. Indeed, much economic analysis presumes that marketing is just as important as R&D in the creation and delivery of innovative health care in the United States today. Economists have demonstrated that manufacturers' provision of information to medical professionals and consumers is an essential component of the business of developing, manufacturing, and distributing drugs in the medical marketplace.[13] As economist Howard Beales observes, "[p]roduction of knowledge about pharmaceutical products is the central objective of pharmaceutical research and development ..."[14]

There are at least three reasons why economists view advertising as such an integral part of the drug development and distribution process. First, marketing educates health-care professionals, caregivers, and patients. Drug companies routinely support the distribution of the newest medical textbook and journal article information to health-care professionals, especially those who prescribe drugs, and thus supplement the professionals' initial medical education. Indeed, much Continuing Medical Education ("CME") and most medical journals would not exist without the support of drug companies through grants and advertising. Moreover, drug detailing by pharmaceutical company specialists provides one-on-one education for doctors by answering their questions and providing critical medical information. Similarly, the newer forms of DTC information have enabled caregivers and patients to learn more about the options available to them, which has empowered consumers to take more control of their own health care, has improved health outcomes, and has created economic benefits for consumers and society.

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consumers may find useful in choosing a lawyer, they may inhibit competition and informed consumer choice . . . Truthful, non-deceptive advertising promotes competition and consumer choice.'").

[13] *See, e.g.*, John E. Calfee, *Prices, Markets, and the Pharmaceutical Revolution* 23-31 (2000).

[14] J. Howard Beales, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 Seton Hall L. Rev. 1370, 1370 (1994).

Second, marketing speeds the diffusion of innovation in health care. Company-sponsored CME, journal advertising, and detailing all jump-start circulation of new information about new drugs on the market, thus accelerating their use in doctors' offices and other patient-care centers. This enables doctors to prescribe new medications when appropriate and expedite patient recovery.

Third, marketing spurs innovation itself. By increasing the sales that fund the entire range of functions that support the drug industry, including R&D, marketing enables research-based pharmaceutical manufacturers to more quickly recover R&D costs, thereby allowing these drug makers to devote additional resources to develop new products. This is a particularly critical benefit of marketing because unlike most branded products, approved drugs have an effective patent life of just under twelve years – which leaves research-based companies a very short period of time to recover the costs and profits necessary to fund the R&D for additional innovative products.[15] Thus, regulators should be particularly careful not to disturb this dynamic synergy between marketing and R&D because suppression of advertising would likely decrease the development of further dramatic breakthroughs in drug treatment.[16]

2. The Continuing Centrality of the Learned Intermediary

In determining that certain drugs should be available only through prescription, FDA has concluded that the safe and effective use of those drugs requires diagnostic and scientific expertise not possessed by the average consumer.[17] Powerful chemical and biological entities

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[15] *See* Henry G. Grabowski & John M. Vernon, *Effective patent life in pharmaceuticals*, 19 Int. J. Tech. Mgmt. 98, 108-109 (2000). For pharmaceutical patents on new chemical entities that received FDA approval between 1984 and 1989, the mean effective patent life was 10.8 years. For those approved between 1990-1995, the average effective patent life was 11.7 years.

[16] John A. Calfee, *The Role of Marketing in the Pharmacological Progress*, Pharmacoeconomics 11-13 (forthcoming) (unedited version, Aug. 11, 2002).

[17] *See* 21 U.S.C. § 353(b).

inevitably pose some health risk in large patient populations; it is logical and appropriate for the government to conclude that treatment of a specific patient requires expert analysis of that patient's condition, consideration of available treatment alternatives, and a thorough understanding of drug choices. While DTC advertising can assist patients in recognizing that certain medical conditions can be treated under a doctor's care, Pfizer believes that protection of the public health requires a system in which the responsibility and authority for choosing drug therapies rests with learned intermediaries. The company's DTC advertising is intended to enhance the relationship between patients and physicians and, at the same time, to make clear to consumers that consultation with a doctor is critical to successful treatment.

Pfizer recognizes that some have expressed concerns about DTC advertising potentially complicating or impairing the doctor-patient relationship. Indeed, even some courts have concluded mistakenly that DTC advertising signals an intent that consumers can forego reliance on their doctor's expertise in administering particular products and venture into making prescribing decisions on their own.[18] Pfizer believes that such decisions distort the role of DTC ads, undervalue the proper responsibilities of learned intermediaries in the health-care system, and misread the empirical evidence on the actual impact of DTC advertising. As FDA itself recognized when it revised its DTC broadcast advertising guidelines in 1997, direct or indirect efforts to suppress or deter DTC advertising are adverse to the public health.[19]

One of the strongest supporters of DTC advertising is a sister agency of FDA – the Federal Trade Commission ("FTC"). In a staff report filed in early 1996 in FDA's DTC

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[18] *See e.g., Perez v. Wyeth Labs., Inc.*, 734 A.2d 1245 (N.J. 1999) (creating a direct-to-consumer advertising exception to the learned intermediary doctrine and noting the existence of a rebuttable presumption that manufacturer has satisfied its duty to warn when it complies with FDA regulations).

[19] FDA, *Guidance For Industry, Consumer-Directed Broadcast Advertisements* (Aug. 6, 1999), *available at* http://www.fda.gov/cder/guidance/1804fnl.htm (finalizing 1997 draft guidance).

advertising proceeding, the FTC found that such ads not only served as "a unique source of some information that can enhance consumer welfare"[20] but actually enhanced the doctor's role as learned intermediary by encouraging consumers to seek out their physicians' advice. Summarizing those benefits, the FTC said:

> Advertising may make consumers aware of more convenient or otherwise more desirable versions of drugs than they currently use. Advertising may encourage consumers to see a doctor for advice about conditions they might have previously ignored or for further information about conditions already being treated. Advertising may cause consumers to inquire about diagnostic tests that might not otherwise be performed. Better informed consumers will be better able to understand and discuss their individual needs with their doctors and pharmacists. Thus, advertising can help consumers make decisions about their health care and health-care costs.[21]

Significant behavioral research on the value of DTC advertising in the late 1990s corroborates FTC's view. FDA itself sponsored two of the best of these studies, which collectively have provided the following findings:

- 64% of consumers agree that DTC ads provide a valuable service in educating the public.[22]
- 61% of consumers agree that DTC ads alert them to symptoms that may be serious.[23]
- 66% of consumers agree that DTC ads increase awareness of new treatment options.[24]
- A majority of consumers agree that DTC ads provide the information they need to ask their doctors about product risks (62%) and benefits (68%).[25]

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[20] Comments of the staff of the Bureau of Economics and the Bureau of Consumer Protection of the Federal Trade Commission, In RE: Direct-to-Consumer Promotion, January 11, 1961, at 3.

[21] *Id.* at 13.

[22] Market Measures Interactive, *DTC Monitor: A Competitive Evaluation of DTC Advertising Campaigns – Analytical Report* 1 (2001).

[23] Scott-Levin, *Direct to Consumer Advertising Audit*, at 2 (3d Qtr. 2001).

[24] *Id.*

- 51% of consumers who see a DTC ad search for more information about a condition or treatment due to the ad.[26]
- 60 million consumers speak to a doctor each year because of a DTC ad – and of these, 25 million speak to a doctor about a condition for the first time.[27]
- 79% of patients who have spoken to a doctor about an advertised medicine report that their doctor was "very willing" to discuss it.[28]
- Physicians report positive impacts of DTC ads based on actual patient interactions.[29]
- 61% of physicians report that DTC advertising has a beneficial effect on their interactions with patients, compared to only 15% who report negative effects.[30]
- 85% of physicians report that patients inquire about products that were appropriate for them.[31]
- The vast majority of physicians report a positive reaction to patient requests. Further, nearly 70% of physicians who receive a request report feeling little or no pressure to prescribe.[32]

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[25] Prevention Magazine, *Fifth Annual Survey of Consumer Reaction to Direct-to-Consumer Advertising of Rx Medicines* (2002).

[26] Office of Medical Policy, Division of Drug Marketing, Advertising, and Communications, *Attitudes and Behaviors Associated with Direct-to-Consumer (DTC) Promotion of Prescription Drugs – Main Survey Results* (1999), *available at* http://www.fda.gov/cder/ddmac/dtcindex.htm; *see also* Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, *Assessments of Physician and Patient Attitudes toward DTC Advertising of Prescription Drugs* (2002), *available at* http://www.fda.gov/cder/ddmac/dtcindex.htm.

[27] Prevention Magazine, *supra* note 25. A 2002 FDA study also confirms the ability of DTC advertising to prompt new diagnosis: 18% of respondents who discussed a condition with their doctor reported that DTC advertising motivated them to talk to a physician about a condition for the first time. FDA, Division of Drug Marketing, Advertising, and Communications, *Direct-to-Consumer Advertising of Prescription Drugs: Preliminary Patient Survey Results* (Apr. 18, 2002), *available at* http://www.fda.gov/cder/ddmac/DTCnational2002a/sld028.htm (hereinafter "2002 Survey").

[28] Prevention Magazine, *supra* note 25. The 2002 FDA survey found that 93% of patients who had a conversation with their doctor about a prescription drug said that their doctor welcomed the question and 83% said the doctor reacted as if the question were a normal part of the visit. *See* 2002 Survey at http://www.fda.gov/cder/ddmac/DTCnational2002a/sld031.htm.

[29] Market Measures Interactive, *supra* note 22 (summarizing physician reports on over 400 office visits where patients initiated a discussion about a prescription drug).

[30] *Id.* at 5.

[31] *Id.* at 14.

- Consumers who request a drug because of DTC advertising are much more likely to comply with the drug regime prescribed by their doctors than those who do not make drug requests.[33]

In light of the extensive evidence of DTC advertising's value in both educating consumers on health-related conditions and enhancing the doctor's professional role in diagnosing and treating those conditions, it is no wonder that an official from FDA's Division of Drug Marketing, Advertising, and Communication ("DDMAC"), in a July 2001 Senate Commerce Committee hearing, made the following understated observation: "At present, FDA is not aware of any evidence that the risks of DTC promotion outweigh its benefits."[34] Even former FDA Commissioner David Kessler admitted that he was wrong to oppose DTC advertising during his tenure and now believes that "there is a lot of educational benefit" provided by the ads.[35]

In short, there is no incompatibility between DTC advertising and a prescription drug regime administered by learned intermediaries. The evidence irrefutably shows that DTC advertising enhances the well-established operation of FDA's prescription drug regime.

C. FUNDAMENTAL CHANGES IN THE SPEECH-RELATED ENVIRONMENT

Pfizer's First Amendment analysis of FDA's speech-restrictive regulations and guidances recognizes and relies upon three pivotal changes in the health-care information environment.

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[32] *Id.* at 20.

[33] Pfizer, Inc. in partnership with RxRemedy, Inc., *Impact of DTC Advertising Relative to Patient Compliance* (2001), *available at* http://www.pfizer.com/pfizerinc/policy/dtcadsdoc.html.

[34] Statement of Dr. Nancy M. Ostrove, Deputy Director of DDMAC, before the Subcommittee on Consumer Affairs, Foreign Commerce and Tourism (July 24, 2001), *available at* http://www.fda.gov/ola/2001/drugpromo0724.html.

[35] Raja Mishra, *Ex-FDA Chief Recants on Drug Advertising*, Boston Globe, Apr. 17, 2002, at A2.

1. Constitutional Protection of Commercial Speech

FDA's principal statutory authorities, including its direct regulatory authority over drug labeling and prescription drug advertising, were conferred at a time when commercial speech was not analyzed with constitutional restraints in mind.[36] Even after the Supreme Court in 1976 overturned an earlier ruling that commercial speech was not protected under the First Amendment,[37] FDA continued to ignore First Amendment proscriptions on the assumption that the "greater power" to regulate pervasively the manufacture and distribution of foods and drugs necessarily included the "lesser power" to regulate all communications related to the regulated activity.[38] Moreover, the agency took the position that communications relating to drugs requiring premarketing approval could be deemed "inherently misleading" and outside First Amendment protection unless FDA had reviewed and cleared them.[39] Under these assumptions, FDA shaped rules and guidances that gave no weight to First Amendment limits on government power (beyond some inkling that the agency's speech mandates might have a spillover effect on purely scientific discourse).

The Supreme Court's decision in *Thompson v. Western States Medical Center*[40] – following upon federal court rulings in *Pearson v. Shalala*[41] and *Washington Legal Foundation*

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[36] *Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942).

[37] *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 757 (1976).

[38] *Posadas de Puerto Rico Assocs. v. Tourism Co. of P.R.*, 478 U.S. 328, 345-46 (1986).

[39] *See Edenfield v. Fane*, 507 U.S. 761, 767 (1993) ("But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.").

[40] 122 S. Ct. 1497 (2002).

[41] 164 F.3d 650 (D.C. Cir. 1999).

v. *Friedman* ("*WLF*")[42] – leave no doubt that FDA restrictions on the flow of information from manufacturers to prescribers and consumers is fully subject to First Amendment review. The concept that the "greater power includes the lesser" for First Amendment purposes was definitively overturned by the Supreme Court in *Greater New Orleans Broadcasting Ass'n v. United States.*[43] Moreover, both that concept and the "inherently misleading" notion were soundly rejected in the *WLF* litigation.[44] Thus, as FDA's Request itself acknowledges, the regulatory scheme must be assessed anew under today's governing First Amendment principles.

2. The Increasingly Multi-Source Information Environment

Existing FDA regulation concerning labeling and advertising was built on two, now outdated premises: (a) that controlling the flow of information from regulated manufacturers about their products would necessarily control the information physicians and consumers received about those drugs, and (b) that manufacturers should bear the burden of conveying balanced, risk-oriented information in all overtly promotional statements about their drugs, whether or not the messages were false and deceptive, because neither doctors nor lay people would otherwise appreciate the relevant risks.

The information environment with respect to pharmaceutical products, particularly prescription drugs, is no longer what the agency once envisioned. Medical journals have proliferated and are widely disseminated on the Internet. Patient advocacy groups track drug developments and regularly provide doctors and consumers with their own evaluations of such products. Health Maintenance Organizations, Pharmacy Benefits Managers and even state

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[42] 13 F. Supp. 2d 51 (D.D.C. 1998), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

[43] 527 U.S. 173, 193-94 (1999).

[44] *WLF*, 13 F. Supp. 2d at 61, 66-67.

Medicaid administrators pursue their own economic interests in affecting prescribing behavior by developing economically incentivized formularies and seeking to persuade physicians that lower cost drugs are preferable. Makers of over-the-counter drugs and dietary supplements advocate their products as effective substitutes for prescription drugs, without confronting the same burdens of detailed regulation or prior review by the government. Even the government has added its voice to the public health debate, launching a year-long DTC advertising campaign extolling the virtues of generic drugs.[45] The result is a multi-source, increasingly adversarial information environment for prescription drugs that conforms to the First Amendment paradigm for a marketplace of ideas.[46] The facts preclude FDA from resorting to any concept of "information market failure" to justify unduly restrictive speech regulation.

In fact, it is not uncommon for prescription drugs to become the focus of public debate in which both their risks and benefits are called into question.[47] Pharmaceutical manufacturers, as directly affected parties and the best informed sources on the scientific evidence concerning their products, should be entitled to play an advocacy role in such controversies. Regulations that would inhibit manufacturers' ability to respond as advocates in public debate initiated by others – either by foreclosing certain channels to them or by obligating them to provide information that dilutes their message – unduly burden their speech rights. These unnecessary speech restraints

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[45] Kim Dixon, *FDA Set To Join In Education Blitz on Generic Drugs* (Aug. 23, 2002), *available at* http://www.forbes.com/newswire/2002/08/23/rtr703823.html.

[46] In fact, there is recent empirical evidence that 72% of patients treated with prescription drugs obtain information about those drugs from books, 69% obtain information from family and friends, 60% from television programs and 18% from the Internet. *See* Mike Magee, *Evolution of the Patient-Physician Relationship in the United States*, *in* paper presented to the World Medical Association, Geneva, Switzerland, at 3 (Apr. 13, 2002).

[47] *See, e.g.,* Marc Kaufman, *Hormone Replacement Gets New Scrutiny: Finding of Increased Risks Prompts Federal Effort,* Wash. Post, Aug. 14, 2002, at A1 (discussing reassessment of risks and benefits of hormone replacement therapy used by post-menopausal women after study finding serious side effects).

also disserve the public because they hamper the vigorous debate from which truth best emerges.[48]

3. Evolving Concepts of Consumer/Physician Communication and Informed Consent

FDA's regulation of manufacturer speech traditionally has attached limited importance to providing lay consumers with drug-related information. Indeed, the agency effectively suppressed the use of broadcast media to convey such information until five years ago.[49] FDA seemingly viewed additional information flows to consumers as serving little purpose beyond generating irrational demands for unnecessary prescriptions and unfair pressures on physicians.

As discussed above, the premise behind restrictive regulation of DTC information flows is increasingly recognized as empirically unsound.[50] From a more fundamental standpoint, opening drug manufacturer channels of communication to patients supports the concept of informed consent, which has evolved from the experimental and surgical contexts to become the dominant paradigm of modern medicine.[51] While doctors do and should hold final decisional authority over prescription drug choices, patients do and should play an increasingly active role in that process.

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[48] It is particularly important that manufacturers have the right to respond to the competing claims of dietary supplement manufacturers, which may be made without FDA first verifying the claims. The Wall Street Journal recently reported that "half of the dozen top-selling herbal supplements are either useless for their marketed purposes or dangerous." *See* Chris Adams, *The Growing Case Against Herbs*, Wall St. J., Aug. 29, 2002, at D1. Prescription drug manufacturers should be able to point out such findings and contrast them with the extensive safety and effectiveness studies that their own products undergo.

[49] FDA, *Guidance For Industry, Consumer-Directed Broadcast Advertisements* (Aug. 6, 1999), *available at* http://www.fda.gov/cder/guidance/1804fnl.htm (finalizing 1997 draft guidance).

[50] *See supra* Part I.B, at 4-6.

[51] *See, e.g.*, Jonathan D. Moreno, Arthur L. Caplan & Paul Root Wolpe, *Informed Consent, in* 2 Encyclopedia of Applied Ethics 687 (1998) ("'INFORMED CONSENT' has become the legal and philosophical cornerstone of physician-patient relationships.").

Dr. Michael Magee, Senior Medical Advisor at Pfizer, has carefully studied the changes in the doctor-patient relationship over the last two decades. Dr. Magee points out that although trust and information exchange continue to be the hallmarks of the relationship, the medical community must respect the influence of several factors that have lead to great shifts in the nature of that connection. These include "(t)he explosion of science and technology, appearance of a health consumer movement, ... [and the] emergence of the Internet."[52] All of these developments have fostered greater participation by patients in their own health-care decision-making. Informed patients look less to their doctors for authoritarian directives and instead rely on physicians more as providers of both information and professional guidance on the best course of medical action. At the same time, medical ethics scholars suggest that patients must have access to extensive and understandable data sources in order to guide and fully inform physician decisions.[53]

Although paternalism and authoritarianism were largely the norm in health care as recently as 1980, national studies reveal a very different reality in present-day patient care. For example, Dr. Magee notes that more than 90% of physicians currently define the best patient as an educated one.[54] The medical community has increasingly recognized the positive role that DTC advertising can play in a beneficial physician-patient relationship. Three recent studies from prominent professional medical groups are particularly illustrative. In 2000, the American Medical Association concluded that "[i]f used appropriately, direct-to-consumer (DTC)

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[52] Magee, *supra* note 46, at 1.

[53] Moreno et al., *supra* note 51, at 691 ("Patients who are capable of giving informed consent are entitled to information about their condition and about the treatment alternatives, including nontreatment."); *id.* at 690 ("[T]he informed consent ideal implies at least one personal encounter between the physician and the patient in which each strives to integrate what the other has to offer: the doctor his or her scientific information, technical knowledge, and clinical experience, and the patient his or her fears, concerns, values, and goals.").

[54] Magee, *supra* note 46, at 2.

advertising has the potential to increase patient awareness about treatment options and enhance patient-physician communication. Advertising directly to the public educates patients, enabling them to better understand and participate in medical care."[55] In that same year, the National Health Council, a group including the American Heart Association and the American Medical Association, concluded that "DTC is an effective tool for educating consumers and patients about health conditions and possible treatments."[56] More recently, the National Medical Association ("NMA") published a report and related survey indicating that a majority of its largely African-American membership believed that DTC advertising has positive benefits for patients and calling for an increase in DTC ads targeted to African-Americans.[57] The NMA's call is consistent with research showing that African-Americans and other minorities are disproportionately likely to have undetected and untreated conditions, such as elevated cholesterol levels and related heart conditions. Therefore, these groups are likely to be aided by commercial messages raising their awareness of available treatments and stimulating conversations with their doctors.[58]

An educated patient is better able to appreciate the benefits and risks of treatment options and to assist the professional in determining which course of therapy best suits his or her needs. DTC advertising plays a measurable role in boosting consumer "health literacy." It thereby enhances consumers' ability to ask relevant questions of – and provide relevant information to –

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[55] John E. Calfee, *Public Policy Issues in Direct-to-Consumer Advertising of Prescription Drugs*, at 6 (2002) (*quoting* American Medical Ass'n Council on Ethical and Judicial Affairs of the American Medical Ass'n, *Direct-to-Consumer Advertisements of Prescription Drugs,* 55 Food & Drug L.J., at 119-124 (2000)).

[56] National Health Council, *Statement on Direct-to-Consumer Prescription Drug Advertising*, at 1 (2002).

[57] National Medical Ass'n, *African American Doctors Say DTC Ads Raise Disease Awareness, Bolster Doctor-Patient Ties*, at 1-2 (2002) (summarizing results of NMA Survey entitled "To Do No Harm": Survey of the Physicians of the National Medical Association Regarding Perceptions on DTC Advertisements).

[58] John Z. Ayanian, M.D., *Heart Disease in Black and White*, 329 New Eng. J. Med. (No. 9) 656-658 (1993).

their doctors during check-ups and other direct physician/patient interactions (many of which are subject to significant time pressure constraints). Improving the quality of this discourse allows patients to give truly informed consent to the physician's decisions, thus enhancing medical relationships and increasing therapeutic confidence. Regulatory restrictions that seek to suppress information flows to consumers for their own supposed good run contrary to best health-care practices as well as First Amendment principles.[59]

D. STRUCTURE OF PFIZER'S COMMENTS

In the remainder of these comments, Pfizer takes account of critical developments in relevant law and the information marketplace concerning prescription drugs and then applies the appropriate legal analysis to the specific FDA rules and policies that regulate the flow of information from drug manufacturers to doctors and patients. Pfizer's comments address only the prescription drug regime; apart from general principles of constitutional law, this analysis is not directed at FDA's regulation of information flows concerning OTC drugs, food, and dietary supplements.

The company first analyzes the evolution of FDA's regulatory interests and the contemporaneous development of First Amendment jurisprudence, including the commercial speech doctrine. This overview distills those interests that FDA may legitimately advance and those First Amendment principles that FDA must honor in regulating information flows. The latter include constitutional antipathy toward prior restraints on information dissemination and the need for the government to justify any significant speech restraint on the basis of important governmental interests that the restraint directly and materially advances. In justifying a restraint, the government also must consider non-speech regulatory alternatives and the need to

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[59] *W. States*, 122 S. Ct. at 1507-08.

avoid collateral damage to speech whose suppression does not advance the interests justifying the restraint.

Pfizer next undertakes a functional review of each area of FDA's regulatory activity to evaluate existing practices, regulations, and guidances and to determine whether First Amendment principles require modifications. As its lodestar, the company analyzes FDA's interest at each step to determine whether the agency's focus is an operational one, *i.e.*, directly advancing the safe and effective use of prescription drugs, or a supervisory one, *i.e.*, regulating the flow of information relating to lawful uses. In certain cases, Pfizer recommends specific modifications that protect the public from unsafe, ineffective drugs and from false or misleading messages without curtailing essential information flows. The scope of this review extends from the agency's claim-based jurisdictional determinations to its guidance on disseminating information concerning unapproved ("off label") uses of FDA-approved drugs.

Pfizer believes that its systematic analysis responds to all of the questions relating to prescription drugs set forth in FDA's Request. By proceeding functionally in these comments, however, the company believes that its analysis will better assist FDA in reviewing specific elements of the current regime. In the interest of completeness, Pfizer has attached a table that cross-references specific sections of these comments to the questions in the Request.

II. THE REGULATORY AND FIRST AMENDMENT INTERESTS THAT FDA MUST RECONCILE

The heart of all First Amendment analysis is reconciliation of legitimate government interests that can be advanced by direct or indirect limitations on speech with the constitutionally established right to communicate and receive information and ideas free from governmental interference. In this section of its comments, Pfizer first traces the development of FDA's regulatory mission – for the purpose of precisely defining the important public health interests

that FDA is charged with protecting. Pfizer has great respect for these interests and recognizes the agency's critical role in ensuring that only safe and effective prescription drugs with adequate instructions for use reach the American public. This section next briefly outlines the various First Amendment analyses applicable to FDA's regulations and summarizes key operating principles that the Supreme Court has articulated to safeguard core free-speech values, with particular emphasis on cases involving commercial communications. In subsequent sections, Pfizer applies those principles to the major elements of the agency's current regulatory regime to determine whether FDA has struck a constitutionally appropriate balance between advancing its important public health interests and minimizing its regulations' restraints on the flow of prescription drug information.

A. THE EVOLUTION OF FDA'S MISSION AND AUTHORITY OVER THE USAGE AND MARKETING OF PRESCRIPTION DRUGS

FDA's regulatory mission addresses two aspects of prescription drug manufacture and distribution: a commercial component, *e.g.*, misbranding and mislabeling, and a clinical one, *e.g.*, safe and effective use. The brief historical review below reveals that both of these interests have deep and ancient roots that predate the era of the First Amendment's Framers. The continuing vitality of the government's concerns for safe and effective drug usage and fair marketing of such pharmaceuticals supports an interpretation of the First Amendment that accords reasonable weight to those interests.

1. Early Pharmaceutical Regulation

In biblical and other ancient societies, governments routinely intervened in commercial markets to ensure the integrity of transactions by, for example, standardizing and supervising

weights and measures.[60] These societies also recognized the need to qualify those persons – then called apothecaries – who prepared and dispensed products intended to cure disease or enhance health.[61] FDA's powers are the descendants of both government concerns.

The U.S. government's involvement in regulating both the commercial and medical aspects of drug preparation and dispensation traces back to pre-colonial and colonial British regulation of medicine. English law prohibited dishonest commercial practices long before the Pilgrim Fathers sailed to America. As early as the 14th century, English law recognized a cause of action for deceit, which "would lie where a seller of merchandise warranted the quality or character of his merchandise, but later delivered goods of lesser quality."[62] One scholar argues that English law also recognized the closely related tort of trademark infringement – *i.e.*, affixing on one's goods a mark similar or identical to the identifying mark of another seller to mislead purchasers into believing that the goods are as of high a quality as those sold by the mark owner – since as early as the 16th century.[63] English concern for commercial integrity in the marketplace during this era extended to the sales of medicinal products.[64]

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[60] For example, an early Roman criminal provision provided: "If a seller or a buyer tampers with the publicly approved measures of wine, corn, or any other thing, or commits a deception with malicious intent, he is sentenced to a fine of double the value of the thing concerned; and it was laid down by decree of the deified Hadrian that those who had falsified weights or measures should be relegated to an island." Dig. 48.10.32.1 (Marcian, Institutes 14), translated in 4 The Digest of Justinian 8242 at 829a (Theodor Mommsen & Paul Krueger eds., Alan Watson trans., U. Pa. Press 1985) (quoted in Stuart P. Green, *Deceit and the Classification of Crimes: Federal Rule of Evidence 609(A)(2) and the Origins of Crimen Falsi*, 90 J. Crim. L. & Criminology 1087 (2000).

[61] Egyptian records circa 1500 B.C. discuss drug compounding practiced by apothecaries, *see* Kremers & Urdang, *History of Pharmacy: A Guide and a Survey* 387 (1947), and the Bible refers to the same art, *see Exodus* 30:25 ("And thou shalt make it an oil of holy ointment, an ointment compound after the art of the apothecary....").

[62] Keith M. Stolte, *How Early Did Early Anglo-American Trademark Law Begin? An Answer to Schecter's Conundrum,* 88 Trademark Rep. 564, 569 n.27, 593-94 (1998). Early deceit cases also required a "relationship of privity, or at least a relationship of relationship of trust," between the parties. *Id.* at 593, 569 n.27.

[63] *Id.* at 564, 595 (citing Sandforth's Case, Cory's Entries, BL MS. Hargrave 123, Folio 168 (1584)), *reprinted in* J.H. Baker & S.F.C. Milsom, Sources of English Legal History – Private Law to 1750, 615-18 (1986). Sandforth's Case dealt with a clothier who used a mark on his low-quality products similar to that of another famous, high-quality clothier, thereby inducing customers to believe that his goods were of the same quality as those of the other

Early British regulation extended beyond commercial integrity issues to encompass promoting the safe and effective administration of drugs in order to safeguard the public health. In 1518, the Crown began to regulate medical practitioners for the apparent purpose of ensuring the adequacy and reliability of their skills by delegating "examining and licensing powers" over physicians to the Royal College of Physicians.[65] The government later made similar delegations of licensing authority for apothecaries and surgeons to voluntary professional bodies such as the London Society of Apothecaries.[66] In 1632, Parliament made it unlawful for apothecaries to sell drugs without a physician's prescription.[67]

In the rougher and more sparsely populated world of early British America, both professional standards for, and colonial government regulation of, the practice of medicine initially were spotty. Even in America's embryonic stages, however, colonial laws reflected and carried forward Britain's dual interest in regulating both the commercial and public health aspects of drug dispensation. Early records indicate that colonial governments were particularly concerned with protecting the public health from the spread of communicable diseases.[68] For

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clothier. The court found that this type of fraudulent trade practice was actionable under the doctrine of deceit although Mr. Stolte argues that the case "does not appear to fit into the common law action of deceit" because the court relaxed the warranty and privity requirements. Stolte, *supra* note 62, at 585-95 (analyzing case).

[64] *See, e.g.* Stolte, *supra* note 62, at 575 (citing *Singleton v. Bolton*, 99 Eng. Rep. 661 (KB 1783)). Lord Mansfield in *Singleton* stated that "'if the defendant had sold a medicine of his own under the plaintiff's name or mark, that would be a fraud for which an action would lie.'" *Id.* at 575 (quoting *Singleton*, 99 Eng. Rep. at 661 (footnote omitted)). Mr. Stolte reports that the case was "[t]he third reported action for trademark infringement." *Id.* at 575.

[65] Richard Shyrock, *Medical Licensing in America, 1650-1965,* at 7 (1967).

[66] *Id.* In practice, the British recognized apothecaries and physicians, along with surgeons, as three different types of medical providers, although in smaller towns and rural areas their services generally were indistinguishable. *Id.*

[67] Harold B. Gill, Jr., *The Apothecary in Colonial Virginia* 18 (1972).

[68] *See* Nissa Strottman, *Public Health and Private Medicine: Regulation in Colonial and Early National America*, 50 Hastings L.J. 383, 389 (1999); Carl Bridenbaugh, *Cities in the Wilderness: The First Century of Urban Life in America, 1625-1742* 241 (2d ed. 1955) (noting, *e.g*, South Carolina law prohibiting vessels bearing sick passengers from anchoring nearer than one mile east of the shore).

example, Massachusetts authorities in 1730 empowered the colony's General Court to remove smallpox victims from town, in 1731 imposed laws to prevent the concealment of smallpox (by requiring red clothes to be hung on all infected areas), and in 1737 erected a hospital for quarantine purposes.[69]

Britain's practice of licensing medical practitioners took time to take root in the American colonies. Colonial American practitioners of medicine usually lacked the formal school training of many of their British counterparts; learning through apprenticeship was the common road to practice on this side of the Atlantic.[70] (The Americans also maintained the dual physician/apothecary role much longer than did professionals in the United Kingdom.)[71] Despite the lack of general licensing schemes during this era, colonial governments did enact several specific laws governing medical practice. Massachusetts tried as early as 1649 to restrain unskilled or unethical practices by regulating "the activities of '[c]hirurgeons [i.e., surgeons], [m]idwives, [p]hysitians, or others' imployed about the bodye of men...the preservation of life or health."[72] Similarly, the New York General Assembly enacted a medical code in 1684 that borrowed word for word from the rather vague Massachusetts statute.[73]

By the time of enactment of the Constitution, the larger colonies had followed the British Parliament's lead in delegating licensing powers to professional societies or, in some cases,

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[69] Francis Packard, *History of Medicine in the United States* 163 (1963).

[70] Shyrock, supra note 65, at 7.

[71] The American colonies did not separately license apothecaries, in contrast to the practice then prevailing in Britain. Robert C. Derbyshire, *Medical Licensure and Discipline in the United States* 3 (1969).

[72] *See* Shyrock, *supra* note 65, at vii; Derbyshire, *supra* note 71, at 3.

[73] Packard, *supra* note 69, at 169, 176. Colonial officials apparently discovered that enacting a law, and enforcing it, were two different things. *See, e.g.*, Shyrock, *supra* note 65, at vii.

retaining that authority for their courts or other government officials.[74] In 1760, New York City passed the first colonial statute to require a licensing examination to practice medicine.[75] Although the regulatory framework varied by colony or state, the plain trend by that period was – in the words of the 1772 New Jersey legislature – government intervention to combat the "many ignorant and unskilful [sic] persons in Physic and Surgery, to gain a subsistence, do take upon themselves to administer Physic and practice Surgery...endangering the Lives and Limbs of their Patients."[76]

The colonies also were concerned about promoting commercial integrity in drug dispensation. Most notably, a 1722 Virginia statute imposed broad mandates on physicians that apparently were motivated by concerns about fraud, including the bilking of patients for services such as the dispensing of drugs. One statutory section is particularly striking:

> whenever any pills, bolus, potion, draught, electuary, decoction, or any medicine, in any form whatsoever, shall be administered to any sick person, the person administering the same shall, at the same time, deliver in his bill, expressing every particular thing made up therein; or if the medicine administered be a simple, or compound, directed in the dispensatories, *the true name shall be expressed in the same bill, together with the quantities and prices*, in both cases.[77]

The penalty for any physician or apothecary who disobeyed the mandate was a non-suit on any action commenced to collect payment.[78] This precursor of modern drug labeling laws confirms

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[74] *See, e.g.*, Packard, *supra* note 69, at 169; Shyrock, *supra* note 65, at 17, 25 (noting New York City law called for examining board composed of executive branch and court officials).

[75] Shyrock, *supra* note 65, at 17.

[76] Packard, *supra* note 69, at 174. Elsewhere on the American continent, colonial governments controlled by other European nations were beginning to follow similar approaches. For example, the Spanish takeover of Louisiana in 1769 ushered in stricter medicinal laws there: apothecaries could not distribute drugs without a prescription, and were forced to keep track of those who bought poisons. Apothecary Gardens, *The History of Apothecaries, Eighteenth Century,* available at: http://members.tripod.com/apothecarygardens0/eighteenthcentury.htm.

[77] *Id.* at 165 (emphasis added).

[78] *Id.* at 165.

early recognition of a government interest in protecting consumers against false and misleading practices in health care.

In short, colonial history shows that the Framers would have recognized legitimate government interests in ensuring that those who prepared and dispensed medicines were adequately qualified and dealt honestly with their clients. It is also clear that apothecaries and physicians were identified by the manner in which they held themselves out to the public – *i.e.*, on the basis of the claims they made for their skills, services, and products. Those purporting to act as apothecaries and physicians without authorization were subject to punishment. To the extent that enforcement of licensing qualification requirements depended on attaching regulatory consequences to speech involving claims about medical benefit, there is no record to suggest concern that First Amendment freedoms were being compromised.

At the same time, however, there were no government limitations on advertisements about medical practice or the dispensing of medications,[79] and advertisements touting the benefits of commercial medications abounded in the colonial press.[80] Thus, early practice distinguished between regulating medical activities, including licensing the right to engage in them, and the unregulated circulation of truthful information relating to lawful activities. Speech about medical products would have been recognized as an important and ordinary component of the information marketplace at the time of the Constitution and Bill of Rights.

2. State and Federal Regulation in the 19th Century

In the century after independence, states continued to regulate the commercial and medical aspects of drug dispensation. The American Pharmaceutical Association assisted in this

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[79] Strottman, *supra* note 68, at 403-04.

[80] *See, e.g., id.* at 404.

endeavor; in 1869 the association presented model laws for states to use in "regulat[ing] the practice of pharmacy and the sale of poisons and prevent the adulteration of drugs and medicines."[81] In 1881, New Jersey and New York promulgated the first state food and drug adulteration laws.[82] At the end of the century, Virginia enacted the first legislation aimed at curbing both adulteration and misbranding. The Virginia statute addressed misbranded products as those which were "labeled or branded so as to deceive or mislead the purchaser, or purport to be a foreign product when branded so, or an imitation either in package or label of an established proprietary product, which has been trade-marked or patented."[83] State governments also began to regulate advertising during this period, prohibiting the promotion of illegal products and services.[84]

Congress also moved at the federal level during the 19th century to regulate both drug safety and the commercial practices relating to drugs. In the 1848 Drug Importation Act, Congress appointed inspectors to examine imported drugs for adulteration and determine if they should be admitted.[85] This had a limited effect, however, because it only functioned to regulate foreign drug products. In 1872, Congress acted against misleading advertisements, giving the

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[81] Kremers & Urdang, *supra* note 61, at 199.

[82] *Id.* at 200-01.

[83] L.Va. 1899-1900, ch. 655, *cited in* Roseann B. Termini, *The Prevention of Misbranded Food Labeling: The Nutrition and Labeling Education Act of 1990 And Alternative Enforcement Mechanisms*, 18 Ohio N.U. L. Rev. 77, 78 (1991).

[84] *See* Daniel E. Troy, *Advertising: Not "Low Value" Speech*, 16 Yale J. on Reg. 85, 111 n.137 (1999) (*citing* Cal. Penal Code, § 323 (1872); Conn. Gen. Stat. tit. 12, § 150 (1866); Del. Rev. Stat. chap. 98, v. 12, § 6 (1874); Digest of Laws of Fla. ch. 80, § 4 (1881); Iowa Code, § 4043 (1873); Compiled Laws of Kan. ch. 31, § 342 (1885); Ky. Rev. Stat. ch. 28, art. 21, § 4 (1860 & Supp. 1866); Me. Rev. Stat. tit. 11, ch. 128, § 13 (1884); Md. Code art. 30, § 114 (1860); Miss. Rev. Code, § 2605 (1871); Compiled Laws of Nev. § 2498 (1873); N.Y. Rev. Stat., ch. 20, tit. 8, § 53 (1875); Oregon Gen. Laws, Crim. Code, ch. 8, § 661 (1874); Compiled Laws of the Territory of Utah § 2002 (1876); Vt. Gen. Stat. ch. 119, § 7 (1870)).

[85] *Id.* at 190.

U.S. Postmaster General authority to forbid use of mail to "persons operating fraudulent schemes," a law that encompassed drug manufacturers as well as other merchants.[86]

In sum, state and federal actions in the 19th century have both historical and constitutional significance for the current FDA regime. The continuum reveals a steady interest in ensuring the integrity of disclosures about pharmaceutical products and their safe administration, thereby setting the stage for more significant legislation in the next century.

3. Evolution of Modern Federal Regulation

The need for the federal government to step in to preserve both the commercial integrity and safety of drug dispensation became increasingly apparent following the Civil War, when the country shifted from an agricultural to an industrial economy and medical products truly began to move in interstate commerce from all areas of the U.S. into the growing cities.[87] Drug manufacturers were among those calling for federal legislation, appealing to Congress for help in excluding worthless products from the market.[88] Both muckracking journalists and the American Medical Association criticized pharmaceutical abuses – in particular, the sale of worthless or even dangerous drug products as cure-alls.[89] "Patent" medicines such as "Warner's Safe Cure for Diabetes" and other concoctions containing opium, morphine, heroin, and cocaine were widespread and sold without restriction.[90] These ills fed the reform environment of the

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[86] Act of June 8, 1872, ch. 335, 17 Stat. 283 (codified at 39 U.S.C. § 3005 (1994)), *cited in* Daniel E. Troy, *Advertising: Not "Low Value" Speech*, 16 Yale J. on Reg. 85, 111 n.154 (1999).

[87] Wallace F. Janssen, *The Story of the Laws Behind the Labels: Part I, 1906 Food and Drugs Act,* FDA Consumer (1981).

[88] *See* James Harvey Young, *The Long Struggle for the 1906 Law*, FDA Consumer 2 (1981). Manufacturers also pointed to the need for uniform legislation to replace the patchwork quilt drug regulatory system then existing among the states. *See id.*

[89] *See id.* at 4; Janssen, *supra* note 87.

[90] *See* Janssen, *supra* note 87.

early 20th century. Shortly after the new century opened, Congress – spurred on by scandalous revelations concerning practices in the meatpacking industry – exercised its power over interstate commerce "as an aid to State legislation against impure food and drugs."[91]

a. The 1906 Pure Food and Drugs Act

For the first time in American history, the 1906 Act empowered the Department of Agriculture's Bureau of Chemistry (the predecessor of FDA) to protect the public against misbranded or adulterated drugs.[92] The statute's focus was on ensuring the commercial integrity of products sold as drugs by requiring manufacturers to sell pure products and to include accurate labels on their products describing the contents therein. As the House Report accompanying the Act explained:

> The penalties of the bill are aimed at cheats. That which is forbidden is the sale of goods under false pretenses, or the sale of poisonous articles as good food. No honest dealer need fear any provision in the bill. Legitimate trade should welcome its enactment into law. Only those wishing to deceive the public will object to its provision. It simply requires honesty of labeling and the exclusion of injurious added products.[93]

Although the Act offered some protection against commercially dishonest practices in drug marketing, it did little to safeguard the public health by ensuring that drugs were safe and would effectively treat the conditions they claimed to address. Most notably, the 1906 Act contained no threshold screening process through which the government would preclear either the safety or effectiveness of a product before allowing it to be marketed.[94]

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[91] Pure Food and Drugs Act, ch. 3915, §§ 1-13, 34 Stat. 768 (1906) (amended 1912), *repealed by* Fed. Food, Drug, and Cosmetic Act of 1938, ch. 675, §§ 1-902, 52 Stat. 1040.

[92] Pure Food and Drugs Act § 4.

[93] H.R. Rep. No. 59-2118, at 7 (1906).

[94] Kleinfeld et al., *Human Drug Regulation: Comprehensiveness Breeds Complexity*, in Seventy-Fifth Anniversary Commemorative Volume of Food and Drug Law, 242, 243 (Food & Drug L. Inst. ed. 1984).

Even the commercial protections offered by the Act were limited. Until the passage of the "Sherley Amendment" in 1912,[95] the federal government had no remedy against false or even fraudulent claims of therapeutic value so long as the ingredient disclosures on the label were accurate.[96] Even after the passage of the Sherley Amendment, the "false and fraudulent" standard of misbranding for therapeutic claims in labeling was an extremely difficult standard of proof due to the near impossibility of demonstrating fraudulent intent on behalf of manufacturers.[97]

Despite its well-recognized gaps, the 1906 Act did vest the Bureau of Chemistry with responsibility for advancing certain information-related government interests that remain within FDA's purview. First, the Act required the Bureau to demarcate its jurisdiction by identifying articles intended for the cure or mitigation of disease.[98] The Bureau focused this analysis on the claims made by manufacturers – distinguishing, for example, between tobacco products that were not marketed with health benefit claims, and so were left unregulated, and physically analogous tobacco products sold with health claims, which were regulated.[99] By looking to manufacturers' identification of intended uses for their products, the Bureau imposed regulatory burdens on the basis of speech, just as governments had done for centuries in looking to professional representations to identify physicians and pharmacists for regulation. This effect,

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[95] Act of Aug. 23, 1912, ch. 352, § 8, 37 Stat. 416 (1912); *see also* Vincent A. Kleinfeld, *Legislative History of the Federal Food, Drug and Cosmetic Act,* 50 Food & Drug L.J. 65, 66 (1995).

[96] *See United States v. Johnson*, 221 U.S. 488 (1911).

[97] S. Rep. No. 73-493 (March 19, 1934) at 117 ("[T]he present law imposes on the Government the added responsibility of showing that [] claims were made fraudulently . . . [t]his burden is a serious handicap to the effective protection of the public.").

[98] Pure Food and Drugs Act §§ 4, 6.

[99] Bureau of Chemistry, U.S. Dept. of Agriculture, Service and Regulatory Announcements No. 13 (Apr. 2, 1914).

however, was viewed not as a restriction on free speech but a natural consequence of the business identity created by the exercise of that freedom.

Second, the Act required the Bureau to ensure that those making purchasing decisions were fully and fairly informed of what they were buying by the product labeling. By focusing on labeling as the principal vehicle for conveying the key instructional information about how to use a drug, Congress identified legitimate interests in preventing the adverse effects of false and misleading statements about a product's formulation and, post-Sherley, its therapeutic effect. Thus, by the early 20th century, the government had clearly staked out its interest in barring false and deceptive information flows about drugs.

b. Federal Food, Drug And Cosmetic Act (1938)

In 1938, Congress enacted the Federal Food, Drug and Cosmetic Act ("FDCA") and created the Food and Drug Administration[100] – thereby expanding the federal government's drug regulatory role from enforcing honest disclosures about drugs to affirmatively protecting the public from unsafe drugs. The legislation was triggered in large part by more than 100 deaths caused by "Elixir Sulfanilamide," which was marketed as a cure-all but actually contained a sweetened version of a substance widely used in paint, varnish, and antifreeze.[101] Most fundamentally, the FDCA required all new drugs to be tested for safety to FDA's satisfaction before being marketed.[102] Moreover, drugs found to be dangerous to health under the conditions of use set forth in their labeling were defined as adulterated and subject to seizure, regardless of

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[100] Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq.* (1998)).

[101] The drug itself survived a variety of quality and safety checks, but in producing a liquid form the manufacturer failed to test the solvent, diethylene gycol, "[which] had deadly effects on the kidneys. As a result, 107 people, mostly children, died before the product was quickly recalled." The Independent Institute, *FDAReview.org: History of Federal Regulation: 1902-Present, available at* http://www.fdareview.org/history.shtml (visited Sept. 8, 2002).

[102] *See* Federal Food, Drug, and Cosmetic Act § 201(p) (codified as amended at 21 U.S.C. §§ 321(p), 355 (1998)).

whether the ingredients were fully disclosed.[103] FDA also was charged with requiring that manufacturers provide "adequate directions for use" on the product label or risk a misbranding charge.[104]

In the long debate preceding passage of the FDCA, Congress also considered giving FDA the power to take action against unfair and deceptive drug advertising.[105] Ultimately, however, FDA's power over drug information flows was restricted to the product labeling,[106] while the Federal Trade Commission was authorized to review drug advertising under the Wheeler-Lea amendments to the Federal Trade Commission Act.[107]

Conferring an affirmative safety mandate on FDA represented an important expansion of the government's interests concerning drug products. Beyond ensuring only the commercial integrity of the products, as its predecessor agency had done in the past, FDA also was responsible for guaranteeing the safety of those products, both before and after they entered the market. Congress gave FDA the tools to advance this public-health interest by not only keeping unsafe products themselves off the nation's drug-store shelves but also overseeing the key

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[103] Kleinfeld, supra note 95, at 68-69 (*quoting Hearings Before a Subcommittee of the Senate Committee on Commerce,* at 12).

[104] *See* Federal Food, Drug, and Cosmetic Act, § 502(f) (codified as amended at 21 U.S.C. § 352(f) (1998)).

[105] *See* Speech by Mr. Rees, *Pure Food & Drug Bill, reprinted in* Charles Wesley Dunn, Federal Food, Drug And Cosmetic Act at 772 (1937).

[106] Dunn, *supra* note 105 (quoting Committee on Interstate and Foreign Commerce Report, S. Rep. No. 75-2138 (1937)). In the original version of the 1938 Act introduced in the Senate in 1933 and in all subsequent versions of the bill except for the final one, advertising was under FDA's jurisdiction and both advertising and labeling were defined in mutually exclusive directions. Labeling was defined as, "written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. 321(m). Advertising was defined as all representations disseminated to the public in any manner of by any means other than by the labeling, for the purposes of inducing, directly or indirectly, the purchase of food, drugs, devices or cosmetics. *See* S. 1944, 73d Cong. § 2(j) (1933); S. 2000, 73d Cong. § 2(j) (1934); S. 2800, 73d Cong. § 2(j) (1934); S.5, 75th Cong. § 201(j) (1935); S.5, 75th Cong. § 2(o) (1937).

[107] Wheeler-Lea Act, ch. 49, § 4, 52 Stat. 111 (1938).

instructions for use, as set forth on the product's labeling, to assure that the drugs were safely and effectively administered. Thus, in evaluating safety prior to and after initial approval of a new drug, FDA was mandated to review labeling information to assess its "operative" role in conveying accurate instructions on how to use a drug.

In 1951, the Durham-Humphrey amendments gave FDA the additional safety-related authority to determine that a drug could be made available to the public only through the prescription of a licensed medical practitioner.[108] This distribution control provided a practical and reasonable alternative to what might otherwise be an insurmountable task: regulating labeling sufficiently to permit laypersons to determine whether a particular drug – and what dosage – would best treat their health condition. By limiting certain drugs to use under prescription, FDA could conduct its labeling review on the assumption that the usage instructions would be reviewed and applied by prescribing physicians with a sophisticated understanding of health conditions and drug risks. Consumers of prescription drugs would derive their drug use information from these learned intermediaries.

c. The 1962 Kefauver-Harris Amendments to the Federal Food, Drug & Cosmetic Act

Following Congressional hearings investigating the prescription drug industry, a push beginning in 1959 to reform the existing federal drug laws eventually resulted in the 1962 Amendments to the FDCA (the "Kefauver-Harris Amendments").[109] This major legislation

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[108] 21 U.S.C. § 353(b).

[109] *See* Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 Rutgers L. Rev. 883, 896 & n.36 (1996). Senator Kefauver convened hearings in 1959 to investigate the prescription drug industry, and these hearings raised the issue of drug efficacy. The resulting legislation was enacted as the Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. 301 *et seq.* (1998)).

significantly expanded FDA's dual roles in protecting the public health and in promoting commercial integrity in drug dispensation.

Congress moved to amend the 1938 Act following a drug tragedy in Europe – the birth of thousands of deformed babies whose mothers had taken the drug thalidomide, widely used as a tranquilizer or sleeping pill and for relief of morning sickness.[110] The drug had been kept off the market in the United States by Dr. Frances Kelsey, who worked at FDA and had seen articles about the drug in the British press. The fear of such a tragedy occurring in this country, coupled with the role that FDA had played in protecting the public in this instance, served both to highlight the danger that untested drugs represented and to provide justification for expanding FDA's public health mandates.[111]

The principal focus of the 1962 Amendments was the efficacy, or lack thereof, of many drugs that had passed through the safety gate under the 1938 Act. As one expert testifying before Congress explained, "[i]t should be obvious to everyone that insufficient knowledge on the part of the doctor regarding the efficacy of a drug can react to the detriment of a patient just as much as a toxic action by the drug, which the Food and Drug Administration now has the power to regulate."[112] To remedy this, the 1962 Amendments required the agency to affirmatively determine that before a manufacturer could distribute a "new drug"[113] in the

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[110] *See* S. Rep. No. 87-1744, at 40-43 (July 19, 1962). "The need to give the physicians of the FDA adequate time to appraise the safety and effectiveness of drugs is dramatically illustrated by the recent case example of thalidomide. This drug . . . when given to expectant mothers . . . [results] in the deformity of infants called seal limbs." *Id.* at 40.

[111] *See, e.g.*, 108 Cong. Rec. 21,070 (1962) (statement of Rep. Reuss that the thalidomide tragedy highlighted FDA's limited authority to prevent a similar incident in the United States).

[112] S. Rep. No. 87-448, at 187 (1961) (statement of Dr. Dowling).

[113] The definition of "new drug" excluded drugs already on the market which were generally recognized as "safe and effective for use under the conditions prescribed, recommended or suggested" in the product labeling. 21

marketplace, the product was not just safe but also effective for specific uses (or indications) set forth in its labeling.[114] Moreover, the 1962 Amendments effectively left the timing of approval to FDA; this was in contrast to the 1938 Act, which presumed that a product was safe absent agency challenge within a fixed period,.[115] The 1962 Amendments also made it clear that each new indication that a manufacturer claimed for a product would require an independent finding of safety and efficacy – and thus the amended statute now effectively equates new uses and new drugs.[116]

In addition to ushering in FDA's efficacy review, the 1962 Amendments expanded the agency's role in promoting commercial integrity in drug marketing. Testimony before the Kefauver subcommittee had revealed a number of abuses in drug advertising directed to the medical profession.[117] In particular, some drug makers promoted their products for uses they could not fulfill and claimed superiority for them over more effective drugs.[118] To halt these practices, Congress transferred direct regulatory authority over these drugs from the FTC to FDA, thereby consolidating power over prescription drug marketing in a single agency.[119]

U.S.C. § 321(p)(1) (1962). FDA subsequently adopted a procedure to review these drugs for efficacy. 21 C.F.R. § 310.6.

[114] Drug Amendments of 1962 § 102(b) (codified as amended at 21 U.S.C. § 355(b)). FDA also had to reassess drugs approved between 1938 and 1962 to take effectiveness considerations into account.

[115] *See Hoffmann-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890, 892 (D.D.C. 1975).

[116] Drug Amendments of 1962 § 102(a)(1) (codified as amended at 21 U.S.C. § 321(p)(1)).

[117] Thomas A. Hayes, M.D., *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 Food & Drug L.J. 57, 61 (1996).

[118] *Id.*

[119] Drug Amendments of 1962 § 131(a) (codified as amended at 21 U.S.C. § 352(n)); Memorandum of Understanding Between Federal Trade Commission and the Food and Drug Administration, 36 Fed. Reg. 18,539 (Sept. 16, 1971).

The 1962 Amendments expanded the range of FDA's interests and transformed the character of the agency. In order to evaluate efficacy in addition to toxicity through "adequate and well-controlled clinical investigations,"[120] FDA had to expand its scientific capability and its expertise in disease conditions. It thus became a true public health agency. FDA also needed to focus more intensively on the operative instructions accompanying the approved drugs to make certain that they provided sufficient guidance for safe uses in the affected patient population, taking into account contraindications and side effects. In addition, the agency was required to consider how to manage a regime in which drugs were permissibly shipped in commerce for limited approved indications but which physicians could continue to prescribe for other purposes as their discretion.

By the mid-1960s, FDA had completed its evolution into a pervasive and powerful regulatory agency. The 1938 Act conferred substantial power on the agency over manufacturing operations, and the 1962 amendments reinforced and expanded FDA's authority to regulate for medical and commercial purposes.[121] As the scope of the agency's responsibilities grew and its ability to influence manufacturers through informal pressures increased, FDA's interest in regulating information flows also expanded. The introduction of efficacy for specific indications into FDA's regulatory sphere gave the agency more pervasive control over a drug's operative instructions for use. It also enabled FDA to discourage manufacturers from making unapproved efficacy claims that fostered off-label uses and had the effect of deterring manufacturers from bringing those uses on-label. In fact, the agency developed a set of labeling regulations that swept in a broad range of manufacturer communications in addition to the traditional set of

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[120] Pub. L. No. 87-781, 76 Stat. 780.

[121] Wallace F. Janssen, *The U.S. Food and Drug Law: How It Came; How It Works,* 35 Food Drug Cosm. L.J. 132, 134 (1980).

operative instructions – *i.e.*, the package insert, duplicated and widely disseminated through the standard professional tool known as the Physician's Desk Reference ("PDR") – in an effort to manage the clinical process and conform it to FDA findings of efficacy.[122] In addition, Congress' transfer from the FTC to FDA of the power to regulate prescription drug advertising further strengthened FDA's enforcement capability and its statutory ability to use its power over information flows in support of its public health interests.[123]

4. FDA's Developing Risk Management Paradigm As a Viable Regulatory Alternative to Commercial Speech Restrictions

FDA recently has sought to enhance its role in promoting safe and effective drug use with an ongoing approach directed at risk management. This relatively new effort has significant import for the agency's approach to regulating drug marketing. FDA recognizes that its preclearance review and post-approval marketing oversight cannot eliminate all risks surrounding a drug. Consensus is growing that drug risks may only be managed effectively through a systematic approach that addresses those risks at every level of health care and delivery. FDA, with the cooperation of industry and other stakeholders, has embarked on a new risk-management paradigm that relies on mechanisms other than commercial speech restraints to decrease the number of adverse events that patients experience, especially set-backs that result from the lack of useful information, poor patient compliance with operative instructions for using a drug, and medical errors.[124] As discussed below, the goal of FDA's risk management efforts is

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[122] *See, e.g.*, 21 C.F.R. § 202(l)(2) (defining "labeling" to include a variety of materials that do not physically accompany the drug but that do "contain[] drug information" and are supplied by or on behalf of the manufacturer, packer, or distributor "for use by medical practitioners, pharmacists, or nurses.").

[123] Drug Amendments of 1962 § 131(a) (codified as amended at 21 U.S.C. § 352(n)); Memorandum of Understanding Between Federal Trade Commission and the Food and Drug Administration, 36 Fed. Reg. 18,539 (Sept. 16, 1971).

[124] *See* National Academy of Sciences, Institute of Medicine, *To Err is Human: Building a Safer Health System*, 1-15 (National Academy of Sciences, National Academy Press) (2000); Quality Interagency – Coordination Task

enhancing patient safety – and the means is by encouraging more speech, rather than less. These initiatives therefore comport well with the First Amendment.

In 1999, FDA commissioned a Task Force on Risk Management to make recommendations concerning the current system for managing product risks. The resulting report (the "Task Force Report") concluded that a systems framework should be applied to medical product risk management.[125] According to the Task Force Report, such a framework would better integrate all parties involved in risk management, foster better understanding of drug risks, and theoretically support more effective risk interventions.[126] While the roles of some players with respect to risk management in the health-care system are not clearly defined, the Task Force concluded that FDA's role is clearly set forth in the FDCA: the pre- and post-marketing activities that center around the agency's drug approval decisions.[127]

The Report went on to find that FDA's current pre-market review processes successfully identify serious risks, but the Task Force determined that there should be more emphasis on quality assurance in post-marketing review programs.[128] The Task Force also proposed options for better risk communication, such as categorizing the types and severity of risks and tailoring communication activities based on the relative risks. Depending upon the risks posed by a

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Force, *Doing What Counts For Patient Safety: Federal Actions to Reduce Medical Errors and Their Impact* (2000); General Accounting Office, *Adverse Drug Events: The Magnitude of Health Risk is Uncertain Because of Limited Incidence Data* (1999).

[125] U.S. Department of Health and Human Services, Food and Drug Administration, *Managing the Risks from Medical Product Use – Creating a Risk Management Framework: Report To The FDA Commissioner From The Task Force On Risk Management* (1999).

[126] *Id.* at 2.

[127] *Id.* at 3, 82.

[128] *Id.*

specific product, the Report identified a number of other speech-sensitive options that agency could employ to improve its risk management efforts, including:

- Designing and implementing additional mechanisms to obtain post-marketing information (e.g., sentinel sites, prospective product use registries, enhanced links to external databases);
- Enhancing FDA's epidemiological and methodological research activities; and
- Increasing the number of post-marketing risk interventions for products with special risks, such as restricting distribution of products or requiring mandatory educational programs for health-care professionals and patients.

Although some aspects of these recommendations are beyond FDA's statutory authority, the Task Force Report recognizes that the agency is – and can continue to be – most effective in managing drug risks at the pre-approval stage. The Report further acknowledges that better management of drug risks may require other stakeholders in the health-care development and delivery system to institute systemic changes in their own operations.

FDA has taken other important steps toward recognizing the systematic nature of risk management and implementing risk-management programs that do not rely on speech restraints. FDA, academia, and industry are currently working with the Agency for Health Care Research and Quality to implement the Centers for Education and Research on Therapeutics ("CERTs") research program.[129] The CERTs program is designed to conduct research and provide education to advance the optimal use of drugs and other health-care products. The CERTs program grew out of the recognition of harms created by underuse, overuse, adverse events, and medical errors associated with drugs and other health-care products. CERTs research has three major goals: (1) to increase awareness of both the uses and risks of new drugs and drug combinations; (2) to provide clinical information to patients and consumers, health-care providers, pharmacists, etc.;

[129] *See generally* Centers for Education and Research on Therapeutics (CERTs) (Apr. 2002), *available at* http://www.ahrq.gov/path/certs.htm (providing overview of the CERTs program).

and (3) to improve quality while reducing cost of care by increasing the appropriate use of drugs and other health-care products and by preventing their adverse effects and consequences of these effects. Programs such as this are crucial to reducing drug risks – and are likely to be far more effective in serving that goal than limitations on manufacturers' truthful, non-misleading speech about their products.

In implementing the new risk management paradigm, FDA must ensure that risk management methods do not interfere with the important roles of other key players in the health-care system. For both policy and legal reasons, the agency must avoid paternalistic restrictions on information about drug products; FDA would serve no public health goal by denying physicians and patients access to truthful information that can help them determine whether to accept the risks associated with certain drugs.

In particular, FDA must be careful not to interfere with the physician's role as a "learned intermediary." According to FDA's Task Force Report, FDA's primary risk-management activity during the post-marketing period of a drug is to ensure that information is available to health-care professionals who actually manage risks at this stage.[130] The Task Force Report recognized that physicians are capable of verbally informing their patients of concerns about a drug and ensuring compliance via patient education efforts as well as patient monitoring.[131]

Nor should FDA interfere with the important role of pharmacists in promoting health-care safety. The agency has testified to Congress that pharmacists are the "crucial safety link" in

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[130] *See* FDA, *Managing the Risks from Medical Product Use – Creating a Risk Management Framework: Report To The FDA Commissioner From The Task Force On Risk Management*, at 76 (1999).

[131] *Id.*

the drug distribution chain because they provide risk and benefit information to consumers.[132] At least one other federal agency agrees; a 1999 report by the Government Accounting Office on adverse drug events recognized the importance of pharmacists in compliance – and recommended increasing their role in advising doctors on prescription decisions and in monitoring drug therapy to encourage greater patient compliance.[133]

In sum, FDA is quickly developing approaches to drug risk management that recognize the realities of the multi-source information environment surrounding doctors and patients today. The agency's experience promises to provide FDA with valuable new tools with which to advance the government's interest in promoting safe and effective drug use while allowing the agency to reduce its historic reliance on constitutionally questionable restrictions on manufacturer speech to serve that end.

B. FIRST AMENDMENT VALUES AND CONSTRAINTS AFFECTING FDA'S REGIME

During the early and middle years of the 20th century, Congress expanded the set of public health interests that FDA is charged to advance. During the later years of that same century – and on what was until lately a separate track – the Supreme Court has recognized a network of First Amendment values and principles that constrain the government's ability to advance its interests by controlling information flows. Briefly revisiting the relevant case law serves to highlight the boundaries that FDA must honor in fashioning a regime that protects both the public health and freedom of speech.

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[132] Statement by Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration Before the Committee on Health, Education, Labor and Pensions, 105th Cong. (2000).

[133] General Accounting Office, *Adverse Drug Events: The Magnitude of Health Risks Is Uncertain Because of Limited Incidence Data* (1999).

Recognized as one of "the preeminent rights of Western democratic theory," freedom of speech is the "touchstone of individual liberty."[134] For that reason, the First Amendment guarantees the right to communicate and receive information free from governmental interference by providing that Congress "shall make no law ... abridging the freedom of speech." Administrative agencies implementing congressional enactments must do so in a manner that is consistent with the First Amendment.[135]

First Amendment values are both personal and societal. On a personal level, "[t]he constitutional right of free expression is ... intended to remove governmental restraints from the arena of public discussion ... in the belief that no other approach would comport with the premise of individual dignity and choice upon which our political system rests."[136] On a societal level, freedom of speech ensures that citizens have access to information with which they can, *inter alia*, educate themselves about political, scientific, social, or other issues of the day, expose government corruption, or make informed decisions concerning the products they purchase.[137] As such, freedom of speech "serves significant societal interests wholly apart from the speaker's

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[134] 4 Ronald D. Rotunda & John E. Nowak, *Treatise on Constitutional Law: Substance and Procedure* § 20.2, at 243 (3d ed. 1999); *see also Cox v. Louisiana*, 379 U.S. 559, 574 (1965) (characterizing freedom of speech as a "basic and fundamental" right); *Palko v. Connecticut*, 302 U.S. 319, 327 (1937) (describing freedom of speech as the "matrix, the indispensable condition, of nearly every other form of freedom"), *overruled on other grounds sub nom. Benton v. Maryland,* 395 U.S. 784 (1969).

[135] *See, e.g., Continental Air Lines, Inc. v. DOT*, 843 F.2d 1444, 1455-56 (D.C. Cir. 1988) ("[I]t cannot be gainsaid that, in carrying on its interpretive function, an agency must be mindful of the higher demands of the Constitution.").

[136] *Simon & Schuster, Inc. v. Members of the N.Y. State Crime Victims Bd.*, 502 U.S. 105, 116 (1991).

[137] *See Pacific Gas & Elec. Co. v. Pub. Utils. Comm'n*, 475 U.S. 1, 8 (1986) (observing that First Amendment "protects the public's interest in receiving information" (citations omitted)); *Kleindienst v. Mandel*, 408 U.S. 753, 762 (1972) ("[I]t is now well established that the Constitution protects the right to receive information and ideas." (quoting *Martin v. City of Struthers,* 319 U.S. 141, 143 (1943))).

interest in self-expression"[138] and thus "protects interests broader than those of the party seeking their vindication."[139]

The personal right to speak out is not compromised by the fact that the speaker is a corporate person or by the speaker's pursuit of commercial advantage.[140] This holds no less true for the manufacturers that FDA regulates: they may assert First Amendment rights,[141] and the value of the information and ideas that they wish to convey is not denigrated by their commercial interest.[142] As the Supreme Court made clear only three years ago, "[e]ven under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtual identical messages are in serious tension with principles undergirding the First Amendment."[143]

Perhaps the most fundamental First Amendment value of all is the avoidance of censorship through pre-screening of individual communications.[144] Regardless of whether a

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[138] *Pac. Gas & Elec. Co.* 475 U.S. at 8.

[139] *First Nat'l Bank of Boston v. Bellotti*, 435 U.S. 765, 776 (1978).

[140] *Id.* at 784 (observing that First Amendment does not support "the proposition that speech that otherwise would be within the protection of the First Amendment loses that protection simply because its source is a corporation"); *accord Greater New Orleans Broad. Ass'n v. United States*, 527 U.S. 173, 191 (1999) ("Government presents no convincing reason for pegging its speech ban to the identity of the owners or operators of the advertised casinos."); *Pac. Gas & Elec. Co.*, 475 U.S. at 16 ("[W]e have held that speech does not lose its protection because of the corporate identity of the speaker."); *N.Y. Times Co. v. Sullivan*, 376 U.S. 254 (1964) (corporate publisher of paid advertising accorded equal rights to public advocate advertiser); *Cent. Hudson Gas & Elec. Corp. v. Pub. Service Comm'n*, 447 U.S. 557, 580 (1980) ("[T]he economic motivation of a speaker [should not] qualify his constitutional protection.") (Stevens, J., and Brennan, J., concurring in judgment).

[141] *Thompson v. W. States Med. Center*, 122 S. Ct. 1497, 1509 (2002) (declaring unconstitutional FDAMA provisions prohibiting drug providers from advertising and promoting particular compounded drugs).

[142] *Bellotti*, 435 U.S. at 777 ("The inherent worth of the speech in terms of its capacity for informing the public does not depend upon the identity of its source, whether corporate, association, union or individual.").

[143] *Greater New Orleans Broad. Ass'n v. United States*, 527 U.S. 173, 193-94 (1999) (citations omitted).

[144] *See Near v. Minesota*, 283 U.S. 697, 713 (1931) ("[I]t has been generally, if not universally, considered that it is the chief purpose of the guaranty to prevent previous restraints upon publication.").

communication has value or even may ultimately be subject to sanction as false, misleading or libelous, "prior restraints on speech and publication are the most serious and the least tolerable infringement on First Amendment rights."[145] Indeed "[a]ny prior restraint on expression comes to th[e] Court with a 'heavy presumption' against its constitutional validity. The government carries a heavy burden of showing justification for the imposition of such a restraint."[146] Although the Court hinted in earlier cases that the prior restraint doctrine may apply with less force to commercial speech than to non-commercial speech[147] and that "a system of previewing advertising campaigns" (*i.e.*, a prior restraint) might be an appropriate regulatory measure in certain circumstances, FDA should consider such measures as a last resort, rather than the first, given the Court's consistent antipathy toward censorship. Accordingly, even if the agency believes that its objectives would be more efficiently advanced by preclearance of manufacturer promotional communications, FDA must be prepared to rely on *ex post facto* review of such speech. The Constitution affords the agency scope, however, to devise safe-harbor incentives that would encourage but not command advance consultation.

FDA also must recognize the value that the First Amendment places on a marketplace of ideas where listeners, rather than the government, evaluate the quality of a speaker's information

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[145] *Nebraska Press Ass'n v. Stuart*, 427 U.S. 539, 559 (1976).

[146] *Org. for a Better Austin v. Keefe*, 402 U.S. 415, 418-19 (1971).

[147] *See Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 771 n.24 (observing that "the greater objectivity and hardiness of commercial speech" may "make inapplicable the prohibition against prior restraints"); *accord Cent. Hudson,* 447 U.S. at 571 n.13 ("We have observed that commercial speech is such a sturdy brand of expression that traditional prior restraint doctrine may not apply to it."). *Compare Nutritional Health Alliance v. Shalala*, 144 F.3d 220 (2d Cir. 1998) (upholding prior restraint on dietary supplement claims) *with Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (rejecting restraint on dietary supplement claims in favor of less speech-restrictive use of disclaimers and disclosures unless FDA could demonstrate that "evidence in support of a claim is outweighed by evidence against the claim" or that "disclaimers similar to the ones [the court suggested] would bewilder consumers and fail to correct for deceptiveness").

and opinion.[148] Perhaps it was inevitable that FDA, as a public health agency with substantial expertise and a dedication to the public interest, would believe that it could enhance the flow of information about prescription drugs by suppressing what it deems to be useless messages and dictating disclosure of what it deems to be useful data. Yet the courts have consistently rejected government paternalism as a justification for restraints on truthful and non-misleading commercial speech – beginning with the seminal case of *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.* and continuing through a 26-year line to *Western States*.[149] It is noteworthy that government regulators in both cases relied, at least in part, on public health concerns as reasons for suppressing truthful, non-misleading speech about drugs.[150] Nevertheless, the Court in *Virginia Pharmacy* emphatically repudiated the state's "highly paternalistic approach" to protecting its citizens that "rests in large measure on the advantages of

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[148] *See 44 Liquormart Inc. v. Rhode Island*, 517 U.S. 484, 503-04 (1996) (quoting *Edenfield v. Fane*, 507 U.S. 761, 767 (1993) ("But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.")).

[149] *See Va. State Bd. of Pharmacy*, 425 U.S. at 757; *W. States*, 122 S. Ct. at 1507 ("We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions."); *id.* at 1503 (characterizing *Virginia State Bd. of Pharmacy* as "the first case in which we explicitly held that commercial speech receives First Amendment protection"); *Greater New Orleans*, 527 U.S. at 195 ("respondents cannot overcome the presumption that the speaker and the audience, not the Government, should be left to assess the value of accurate and nonmisleading information about lawful conduct"); *44 Liquormart*, 517 U.S. at 503 ("The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good."); *Edenfield v. Fane*, 507 U.S. 761, 767 (1993) ("[T]he general rule is that the speaker and the audience, not the government, assess the value of the information presented."); *Riley v. Nat'l Fed'n of the Blind of N.C.*, 487 U.S. 781, 790-91 (1988) (rejecting State's "paternalistic premise that charities' speech must be regulated for their own benefit" and finding that "First Amendment mandates that we presume that speakers, not the government, know best both what they want to say and how to say it"); *Cent. Hudson*, 447 U.S. at 562 (citing *Va. State Bd. of Pharmacy*, 425 U.S. at 761-62); *Bellotti*, 435 U.S. at 791 n.31 ("The First Amendment rejects the 'highly paternalistic' approach of statutes ... which restrict what people may hear." (quoting *Va.State Bd. of Pharmacy*, 425 U.S. at 770)); *Va. State Bd. of Pharmacy*, 425 U.S. at 773 ("[A] State may [not] completely suppress the dissemination of concededly truthful information about entirely lawful activity, fearful of that information's effect upon its disseminators and its recipients.").

[150] *See W. States*, 122 S. Ct. at 1504-05 (acknowledging the government's asserted interest in protecting the public health through preservation of the new drug approval process and the availability of compounded drugs); *Va. State Bd. of Pharmacy*, 425 U.S. at 767 (noting Board's argument that price advertising "will place in jeopardy the pharmacist's expertise and, with it, the customer's health.").

their being kept in ignorance" of "entirely lawful terms that competing pharmacists are offering."[151] Similarly, the Court in *Western States* rejected FDA's argument that a restriction on compounded drug advertising was required because such advertising would "put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway."[152] "[A] fear that people would make bad decisions if given truthful information" cannot validate a speech regulation,[153] no matter how laudable the goal or well-intentioned the regulator might be. The Court went on to repeat *Virginia Pharmacy's* now-classic explication of the required "alternative to [the] highly paternalistic approach":

> That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.... But the choice among these alternative approaches is not ours to make or the Virginia General Assembly's. It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us.[154]

Closely related to the First Amendment's rejection of paternalism is the presumption that truth will best emerge from the collision of ideas that results from open channels of communication.[155] This concept holds true for prescription drugs, where FDA has increasingly recognized in its risk management program that scientific truth relating to the use of prescription drugs is not fixed and must be adjusted as evidence accrues. Moreover, given the benefit and

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[151] *Va. State Bd. of Pharmacy*, 425 U.S. at 769-70.

[152] *W. States*, 122 S. Ct. at 1507.

[153] *Id.*

[154] *Id.* at 1508 (*citing Va. State Bd. of Pharmacy*, 425 U.S. at 770).

[155] *See, e.g., Whitney v. California*, 274 U.S. 357, 377 (1927), *overruled in part, Brandenburg v. Ohio*, 395 U.S. 444 (1969) ("[T]he remedy to be applied is more speech, not enforced silence. Only an emergency can justify suppression.").

risk calculus involved in the use of any drug, there is ample room for public debate over drug use and constitutional value in letting all speakers play an equal role in that debate.[156]

First Amendment precedent favoring the curative power of "more speech" gives value to FDA disclosure requirements as an alternative to suppression and an antidote to potentially misleading impressions. Although "[t]here is necessarily, and within suitably defined areas, a concomitant freedom *not* to speak publicly, one which serves the same ultimate end as freedom of speech in its affirmative aspect,"[157] the Supreme Court has indicated that "[p]urely commercial speech is more susceptible to compelled disclosure requirements" than is noncommercial speech[158] due to its "greater objectivity and hardiness."[159] Thus, as between suppressing certain commercial messages altogether and permitting them with mandatory disclosures to guard against fraud, the First Amendment supports the use of disclosure requirements in the first instance:[160]

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[156] *Greater New Orleans*, 527 U.S. at 193-94 ("[e]ven under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtually identical messages are in serious tension with principles undergirding the First Amendment") (citations omitted).

[157] *Harper & Row Publishers, Inc. v. Nation Enters.*, 471 U.S. 539, 559 (1985) (emphasis in original) (internal quotations omitted); *Pac. Gas & Elec. Co.*, 475 U.S. at 909 (same); *United States v. United Foods, Inc.*, 533 U.S. 405, 410 (2001) ("Just as the First Amendment may prevent the government from prohibiting speech, the Amendment may prevent the government from compelling individuals to express certain views.").

[158] *See Riley*, 487 U.S. at 796 n.9; *see also, e.g., Va. State Bd. of Pharmacy*, 425 U.S. at 771 n.24.

[159] *Va. State Bd. of Pharmacy*, 425 U.S. at 772 n.24.

[160] *See, e.g., Ibanez v. Fla. Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 145 (1994) ("[C]oncern about the possibility of deception in hypothetical cases is not sufficient to rebut the constitutional presumption favoring disclosure over concealment."); *Bates v. State Bar of Ariz* , 433 U.S. 350, 375 (1977) (holding that "incomplete" attorney advertising was not inherently misleading and that "the preferred remedy is more disclosure, rather than less"); *Pearson v. Shalala,* 164 F.3d at 657-58 (concluding that the commercial speech doctrine embodies a preference for disclosure over outright suppression); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 73 (D.D.C. 1998) ("*WLF*") ("[Disclaimers] comport[] with the Supreme Court's preference for combating potentially problematic speech with more speech."), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

> Because the extension of First Amendment protection to commercial speech is justified principally by the value to consumers of the information such speech provides, appellant's constitutionally protected interest in *not* providing any particular factual information in his advertising is minimal. Thus, in virtually all our commercial speech decisions to date, we have emphasized that because disclosure requirements trench much more narrowly on an advertiser's interests than do flat prohibitions on speech, "warning[s] or disclaimer[s] might be appropriately required ... in order to dissipate the possibility of consumer confusion or deception."[161]

Some tolerance for mandatory disclosure, however, is not a license for FDA to transform manufacturer speech into an involuntary platform for government messages.[162] At a minimum, such requirements must be "reasonably related to the State's interest in preventing deception of consumers"[163] and cannot be applied to the point where they make manufacturer speech impractical.[164]

Finally, given FDA's pervasive network of controls over the businesses of prescription drug manufacturers, the high degree of "expert discretion" inherent in its critical licensing activities, and the absence of adequate "separation of functions" between its supervision of information and advertising and oversight of safety and efficacy,[165] the agency must be

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[161] *Zauderer v. Office of Disciplinary Counsel,* 471 U.S. 626, 651 (1985) (*quoting In re R.M.J.*, 455 U.S. 191, 201 (1982)) (internal citations omitted). This reasoning obviously provides one underpinning for the authority of FDA and other agencies to mandate the substantive information on labels or operational labeling used by the person making the ultimate decision to buy the product, which constitute "affirmative disclosures that the speaker might not make voluntarily." *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 492 n.1 (Stevens, J., concurring); 15 U.S.C. § 1333 (requiring "Surgeon General's Warning" labels on cigarettes); 21 U.S.C. § 343 (1988 ed. & Supp. V) (setting labeling requirements for food products); *id.* § 352 (setting labeling requirements for drug products); *see also* 15 U.S.C. § 77e (requiring registration statement before selling securities).

[162] *See, e.g., Harper & Row,* 471 U.S. at 559 ("There is necessarily, and within suitably defined areas a concomitant freedom *not* to speak publicly, one which serves the same ultimate end as freedom of speech in its affirmative aspect.").

[163] *Zauderer*, 471 U.S. at 651.

[164] *Id.* ("[U]njustified or unduly burdensome disclosure requirements might offend the First Amendment by chilling protected commercial speech").

[165] *See infra* Part II.C.4.a, at 56-59.

especially sensitive to its ability to suppress lawful speech informally. The Supreme Court has expressed continuing concern about even necessarily vague prohibitions that "chill" lawful communications.[166] Thus, First Amendment values counsel that FDA – absent a reform of its internal procedures modeled, for example, on FTC procedures[167] – should err on the side of caution in moving against speech on the valid but inherently vague ground that it is false and misleading.

C. RECONCILING FIRST AMENDMENT VALUES AND PUBLIC HEALTH INTERESTS

There is no single rule or formula for balancing or reconciling legitimate government interests in controlling information flows and First Amendment values. The Supreme Court, however, has provided an extensive analytical framework for the systematic identification, evaluation, and reconciliation of those interests. The precise test for analyzing the constitutionality of the speech restriction at issue hinges on where in the "rough hierarchy in the constitutional protection of speech"[168] the type of speech at issue falls. Yet as a general matter, the analytical factors within each test remain relatively constant: they include the substantiality of the government's interest, the degree to which the regulation effectively advances the government's interest, and the extent to which the regulation targets only the speech that is justifiably regulated. Pfizer now describes the Court's framework as further background to its analysis of the permissible scope of FDA's controls over the flow of information concerning prescription drugs.

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[166] *E.g.*, *Keyishian v. Bd. of Regents*, 385 U.S. 589, 604 (1967).

[167] *See infra* pp. 56-59.

[168] *R.A.V. v. City of St. Paul, Minn.*, 505 U.S. 377, 422 (1992) (Stevens, J., concurring in the judgment).

1. General Rule – Strict Scrutiny

Ordinarily, government attempts to suppress or regulate speech on matters of public concern must survive "strict scrutiny" by the courts.[169] To prevail in strict scrutiny review, the government must prove that its actions further a compelling government interest and that there are no alternative means of advancing that interest that would restrict less speech.[170] As the Supreme Court has recognized, the government rarely, if ever, prevails in strict scrutiny cases.[171] Indeed, while false statements may play no useful role in public debate, the First Amendment even tolerates some risk of falsehood to avoid spilling restrictions over into any protected speech.[172]

The general strict scrutiny rule is not limited to political debate. It has been extended to matters of academic interest[173] and to scientific debate.[174] It is hardly surprising in an era when

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[169] *See, e.g., Republican Party of Minn. v. White,* 122 S. Ct. 2528, 2534 (2002) (applying strict scrutiny to speech concerning qualifications of public office candidates); *Burson v. Freeman,* 504 U.S. 191, 197 n.3 (1992) ("[A] content-based regulation of political speech in a public forum is valid only if it can survive strict scrutiny." (citation omitted)); *R.A.V.,* 505 U.S. at 422 (Stevens, J., concurring in the judgment) ("Core political speech occupies the highest, most protected position . . . ."); *NAACP v. Claiborne Hardware Co.*, 458 U.S. 886, 913 (1982) ("[E]xpression on public issues 'has always rested on the highest rung of the hierarchy of First Amendment values.'" (citation omitted)).

[170] *United States v. Playboy Entm't Group, Inc.*, 529 U.S. 803, 813 (2000) (characterizing "strict scrutiny" test as requiring speech-restrictive regulations to be "narrowly tailored to promote a compelling Government interest" and the least restrictive means of achieving that interest).

[171] *See Miller v. Johnson,* 515 U.S. 900, 920 (1995) (recognizing strict scrutiny as the "most rigorous and exacting standard of constitutional review"); *City of Los Angeles v. Alameda Books Inc.,* 122 S. Ct. 1728, 1745 (2002) (Souter, J, Stevens, J., Ginsburg, J., and Breyer, J., dissenting) ("[S]trict scrutiny leaves few survivors.").

[172] *N.Y. Times Co. v. Sullivan,* 376 U.S. 270, 279-81 (1964) (protecting false statements not made with "actual malice" against libel remedies).

[173] *Keyishian,* 385 U.S. at 603.

[174] *Bd. of Trustees of Leland Stanford Jr. Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ("It is equally settled . . . though less commonly the subject of litigation, that the First Amendment protects scientific expression and debate just as it protects political and artistic expression."); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 62 (D.D.C. 1998) ("*WLF*") ("Scientific and academic speech reside at the core of the First Amendment." (citation omitted)), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part*, 202 F.3d 331 (D.C Cir. 2000); *Miller v. California*, 413 U.S. 15, 34 (1973) ("The First Amendment

scientific disagreement on such critical matters as global warming directly affects our national future that First Amendment values would require fostering and protecting relevant adversarial expression on scientific and academic topics. Indeed, whenever an issue, whether or not once private, is thrown into the public arena, the social interest in open debate makes strict scrutiny constitutionally applicable.[175] Thus, FDA must carefully consider the type of communication that it seeks to regulate in any particular case. The agency must be prepared to face strict scrutiny if it attempts to restrict, for example, scientific exchange on the utility of a drug manufacturer's product or public policy debate on whether certain classes of drugs should be disfavored in government or private formularies. FDA sensitivity for First Amendment values should be acute when such debate is initiated by others.[176]

2. Speech Characterizing Behavior

The broad protection generally afforded to expressive speech, as noted above, is rooted both in concepts of personal liberty and the social value of a marketplace of ideas. Those interests, however, do not reach situations where words are an integral element of unlawful conduct and the government uses them to define or characterize unlawful behavior. For example, if the statement "Put the money in this paper bag and hand it to me" is used to prove that a defendant engaged in a bank robbery, First Amendment interests are not implicated. Similarly, if evidence of oral or written expression is used to establish a race-inspired "hate

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protects works which, taken as a whole, have serious literary, artistic, political, or *scientific* value, regardless of whether the government or a majority of the people approve of the ideas these works represent." (emphasis added)).

[175] *See, e.g., Garrison v. Louisiana*, 379 U.S. 64, 74-75 (1964).

[176] *See, e.g.*, Marc Kaufman, *Hormone Replacement Gets New Scrutiny: Finding of Increased Risks Prompts Federal Effort*, Wash. Post, Aug. 14, 2002, at A1 (discussing reassessment of risks and benefits of hormone replacement therapy used by post-menopausal women after study finding serious side effects).

crime" subject to greater punishment than the same action taken for other reasons, First Amendment interests are not impaired.[177]

This principle holds equally true for commercial speech. As the Court in *Pittsburgh Press Co. v. Pittsburgh Commission on Human Relations* explained, "[a]ny First Amendment interest which might be served by advertising an ordinary commercial proposal and which might arguably outweigh the governmental interest supporting the regulation is altogether absent when the commercial activity itself is illegal and the restriction on advertising is incidental to a valid limitation on economic activity."[178] In such instances, the regulation at issue is subject to the so-called "rational basis" test.[179] Under this forgiving standard, "regulating legislation affecting ordinary commercial transactions is not to be pronounced unconstitutional unless in the light of the facts made known or generally assumed it is of such a character as to preclude the assumption that it rests upon some rational basis within the knowledge and experience of the legislators."[180] FDA therefore has some scope to analyze manufacturer speech about their products – *e.g.*, claims that Laetrile will cure cancer – in order to characterize the market behavior of a manufacturer as selling a drug and to regulate the manufacturer accordingly.[181]

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[177] *Wisconsin v. Mitchell,* 508 U.S. 476 (1993).

[178] 413 U.S. 376, 388-89 (1973) (upholding municipal ordinance forbidding sex-designated help-wanted advertisements where the refusal to interview or hire on a gender-neutral basis would have constituted unlawful employment discrimination).

[179] *See, e.g., United States v. Carolene Prods. Co.*, 304 U.S. 144, 152 (1938) (holding that statute prohibiting the shipment of filled milk in interstate commerce is a constitutional exercise of government power to regulate interstate commerce and was not prohibited by the due process clause of the Fifth Amendment).

[180] *Id.; see also Greater New Orleans Broad., Ass'n v. United States*, 527 U.S. 173, 193 (199) ("It is well-settled that the First Amendment mandates closer scrutiny of government restrictions on speech than of its regulation of commerce alone." (citation omitted)).

[181] *See generally United States v. Rutherford,* 442 U.S. 544, 545 (1979).

3. Speech Incidentally Affected By Restraints on Behavior

As Supreme Court Justice Breyer has pointed out: "Nearly every human action that the law affects, and virtually all governmental activity, involves speech."[182] If the incidental impact on speech of all government regulatory activity were subject to strict scrutiny, the government could be brought to a halt. Thus, the Supreme Court has recognized that where the target of government action is non-expressive conduct, reasonable latitude should be accorded to incidental restraints on expression.[183] In *United States v. O'Brien*, the Court laid out a four-part analysis to determine when "a sufficiently important governmental interest in regulating the nonspeech element can justify incidental limitations on First Amendment freedoms":

> [A] government regulation is sufficiently justified [1] if it is within the constitutional power of the Government; [2] if it furthers an important or substantial government interest; [3] if the governmental interest is unrelated to the suppression of free expression; and [4] if the incidental restriction on alleged First Amendment freedoms is no greater than is essential to the furtherance of that interest.[184]

FDA regulates large areas of prescription drug manufacturer conduct for purposes of the the non-speech goal of promoting safe and effective drug use. Some of the agency's regulatory actions affecting speech, such as review of a drug's operative instructions for use, would likely be deemed incidental to conduct regulation and subject to *O'Brien* flexibility. The Supreme Court's recent decision in *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525 (2001), however,

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[182] *United States v. United Foods*, 533 U.S. 405, 424 (2001) (Breyer, J., dissenting).

[183] *United States v. O'Brien*, 391 U.S. 367, 376 (1968). Where, however, the conduct addressed is itself expressive and the government acts to suppress that expression, strict scrutiny continues to apply. *Texas v. Johnson*, 491 U.S. 397, 407 (1989) (flag burning).

[184] *O'Brien*, 391 U.S. at 377. The Court has frequently upheld regulations under the *O'Brien* standard. *See, e.g., Clark v. Cmty. for Creative Non-Violence*, 468 U.S. 288, 299 (1984) (restrictions on overnight sleeping in federal parks unrelated to suppression of expression but rather designed to protect national park property); *United States v. Albertini*, 472 U.S. 675, 687 (1985) (law prohibiting re-entry onto a military base meant to prevent entry of those whose previous conduct demonstrated a threat to security); *Wayte v. United States*, 470 U.S. 598, 611-13 (1985) (passive enforcement policy for failure to register for the draft furthered government interest in ensuring national security).

requires FDA to exercise caution in assuming that it has *O'Brien* flexibility where the means or substance of expression is a major regulatory concern. In *Lorillard*, the Court disaggregated a group of state restraints on tobacco marketing; it held that physical limitations on teenagers' access to tobacco products (*e.g.*, bars on self-service displays) were reviewable under *O'Brien* and sustainable but that restrictions on the use of outdoor advertising and point-of-sale materials were speech restraints subject to the so-called *Central Hudson* test and ultimately unsustainable.[185] Thus, the mere fact that FDA's controls on the flow of information may ultimately target doctor and consumer conduct does not necessarily afford the agency the latitude of *O'Brien* analysis.

4. Commercial Speech Regulation

For at least 60 years, the Supreme Court has acknowledged the important role of government in regulating the commercial marketplace by subjecting commercial speech to a First Amendment analysis different from its general strict scrutiny test. Although the Court in 1942 ruled that commercial speech was entitled to no First Amendment protection at all,[186] it changed course in its 1976 *Virginia Pharmacy* decision, holding that the First Amendment did extend to commercial speech.[187] Such messages initially were understood to encompass speech that "does no more than propose a commercial transaction,"[188] but the Court later expanded the area of commercial speech analysis to take into account whether (1) the speech at issue is conceded to be an advertisement; (2) the speech refers to a particular product; and (3) the speaker

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[185] *Lorillard,* 533 U.S. at 556-57, 565-67, 569-70.

[186] *Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942).

[187] 425 U.S. 748, 770-71 (1976).

[188] *Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations*, 413 U.S. 376, 385 (1973).

has an economic motive.[189] If examination of these factors shows the speech to be predominantly commercial, then use of a modified First Amendment framework is appropriate.

Since 1980, the Supreme Court's First Amendment scrutiny of commercial speech has adhered to the four-pronged test first set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission.*[190] The threshold analytical question is whether the speech concerns "lawful activity" and is not misleading.[191] Commercial speech that effects or induces an illegal transaction or creates a false basis for commercial transactions is not consistent with an orderly marketplace and can be suppressed without regard to First Amendment concerns.[192] All other commercial speech can be regulated only to advance a "substantial" government interest and only where "the regulation directly advances the government interest asserted" and is "not more extensive than is necessary to serve that interest."[193] The would-be regulator, in this case FDA, bears the burden of establishing that its speech restriction survives *Central Hudson* scrutiny,[194] a burden that the Supreme Court has held is "not satisfied by mere speculation or conjecture."[195]

FDA's controls over information flow plainly encompass a great deal of speech that would be considered commercial under *Bolger*. The agency therefore needs to give careful

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[189] *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66-67 (1983).

[190] 447 U.S. at 566.

[191] *Id.*

[192] *Id.*; *Pittsburgh Press*, 413 U.S. at 388-89.

[193] *Cent. Hudson*, 447 U.S. at 566.

[194] *Bolger*, 463 U.S. at 70 n.20 ("The party seeking to uphold a restriction on commercial speech carries the burden of justifying it.").

[195] *Edenfield v. Fane*, 507 U.S. 761, 770-71 (1993).

attention to the principles that the Supreme Court has established for applying the *Central Hudson* analysis.

a. Prong 1: Not false or misleading

"[O]nly false, deceptive, or misleading commercial speech may be banned."[196] The Court is reluctant to conclude that commercial speech is misleading unless the regulator proffers some evidence to substantiate the claim of deception.[197] "[T]he free flow of commercial information is valuable enough to justify imposing on would-be regulators the costs of distinguishing the truthful from the false, the helpful from the misleading, and the harmless from the harmful."[198] Even when advertising communicates only an incomplete version of the relevant facts, the First Amendment presumes that some accurate information is better than no information at all.[199]

The Court's decision in *In re R.M.J.* suggested that some commercial speech might be found "inherently misleading" and thus subject to suppression without specific evidence:

> [W]hen the particular content or method of the advertising suggests that it is inherently misleading or when experience has proved that in fact such advertising is subject to abuse, the States may impose appropriate restrictions. Misleading

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[196] *Ibanez v. Fla.Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 142 (1994); *see also Peel v. Attorney Registration & Disciplinary Comm'n of Ill.*, 496 U.S. 91, 109 (1990) (referring to the "heavy burden of justifying a categorical prohibition against the dissemination of accurate factual information to the public" (citing *In re R.M.J.*, 445 U.S. 191, 203 (1982))). As previously mentioned, if the speech at issue concerns lawful conduct and is truthful and nonmisleading, the Court has evidenced a strong preference for remedying any potentially misleading aspects of it by requiring the disclosure of additional information, rather than suppressing the speech entirely. *See supra* Part II.B, at 44-46.

[197] *See, e.g., Ibanez,* 512 U.S. at 146 ("[W]e cannot allow rote invocation of the words 'potentially misleading' to supplant the [government's] burden . . . ."); *In re R.M.J.*, 455 U.S. 191 (speech at issue "has not been shown to be misleading"); *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81, 85 (D.D.C. 1999) ("FDA may not restrict speech based on its perception that the speech could, may, or might mislead."), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000); *Pearson v. Shalala*, 164 F.3d 650, 655 (1998) (rejecting argument that health claims were inherently misleading based on lack of "significant scientific agreement").

[198] *Zauderer v. Office of Disciplinary Counsel,* 471 U.S. 626, 646 (1985); *accord Ibanez*, 512 U.S. at 143.

[199] *Cent. Hudson*, 447 U.S. at 562.

> advertising may be prohibited entirely. But the States may not place an absolute prohibition on certain types of potentially misleading information ... if the information also may be presented in a way that is not deceptive.[200]

The Court's more recent decision in *Peel v. Attorney Registration & Disciplinary Commission*,[201] however, cast doubt on the significance of the "inherently misleading" concept. In a plurality opinion, Justice Stevens rejected the Illinois Supreme Court's conclusion that advertising a lawyer's certification as a trial specialist by a non-bar agency was "inherently misleading"[202] and suggested that states could clarify any potentially misleading statements by, for example, requiring disclosures about the certifying organization and/or the standards of a particular specialty.[203]

FDA already has felt the impact of the courts' general antipathy toward an "inherently misleading" argument. For example, in *Pearson v. Shalala*, FDA had argued that health claims for a dietary supplement label were inherently misleading because they failed to meet the threshold requirement of scientific agreement that FDA had established and because the average consumer lacked the necessary ability to evaluate the claims.[204] Although the lower court had accepted FDA's argument,[205] the D.C. Circuit repudiated that notion sharply:

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[200] *In re R.M.J.*, 455 U.S. at 203.

[201] 496 U.S. 91 (1990).

[202] *See id.* at 100-03. Even when a court determines that the speech is inherently misleading, some will nonetheless go on to evaluate the restraint under the full four-part *Central Hudson* test. *See Farrin v. Thigpen*, 173 F. Supp. 2d 427, 441, 445 (M.D.N.C. 2001).

[203] *See Peel,* 496 U.S. at 110. Justice Marshall, in his concurring opinion, clarified that a statement is "inherently misleading" when, despite a lack of evidence of actual deception in the record, "the particular method by which the information is imparted to consumers is inherently conducive to deception and coercion." *Id.* at 112 (Marshall, J. and Brennan, J., concurring). Justice O'Connor, in her dissent, further explained that "inherently misleading" means "inherently likely to deceive the public." *Id.* at 121 (O'Connor, J., Rehnquist, C.J., and Scalia, J., dissenting).

[204] *See* 14 F. Supp. 2d 10, 18-19 (D.D.C. 1998), *rev'd*, 164 F.3d 650 (D.C. Cir. 1999).

[205] *Id.*

> As best we understand the government, its first argument runs along the following lines: that health claims lacking "significant scientific agreement" are inherently misleading because they have such an awesome impact on consumers as to make it virtually impossible for them to exercise any judgment at the point of sale. It would be as if the consumers were asked to buy something while hypnotized, and therefore they are bound to be misled. We think this contention is almost frivolous. We reject it.[206]

The court in *Washington Legal Foundation v. Friedman* ("WLF") rejected a similar FDA argument.[207]

The requirement that the agency find evidentiary support before deeming speech to be false or misleading has an important consequence for FDA's regulatory regime: where the agency wishes to restrain a commercial communication as false or misleading, it should carefully consider the adequacy of its current enforcement procedures. To determine that a communication is "misleading" requires both an interpretation of its message and a comparison of that message to a proven state of "fact." Unlike the FTC, FDA has no established criteria for determining whether communications can be interpreted on their face or require empirical evaluation. Moreover, absent resort to court proceedings, FDA has no record procedure with respect to falsity. These procedural problems highlight a constitutionally significant flaw in FDA's current approach to supervising promotional communications: rather than employ transparent and neutral evaluation procedures that allow for case-specific reviews that best accommodate First Amendment values, the agency has relied on overbroad, categorical speech restraints that are highly restrictive and administered in ways that are not always easy to understand or predict.

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[206] *Pearson*, 164 F.3d at 655 (citation omitted).

[207] 13 F. Supp. 2d 51, 67 (D.D.C. 1998) ("*WLF*") ("In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe."), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

Given FDA's pervasive and discretionary regulatory controls over prescription drug manufacturers, the agency should carefully consider adopting an administrative procedure for processing issues of misleading speech that separates enforcement from adjudicatory responsibilities. In fact, FDA already has such an administrative procedure in place, and its applicability could be broadened to include determinations as to whether particular messages are false and misleading. The agency's regulations currently provide for an informal hearing procedure either where the Commissioner is considering regulatory action and decides "to offer an opportunity for a regulatory hearing to obtain additional information before making a decision or taking action"[208] or generally where the act or regulation affords the opportunity for a hearing on a regulatory action.[209] For example, a regulatory hearing is available with respect to any agency determination that prior approval is required for a prescription drug advertisement for certain dangerous drugs or that a specific advertisement for that drug is not approvable.[210]

These regulatory hearings are not subject to FDA's formal separation of functions rules,[211] set forth in 21 C.F.R. § 10.55. (The latter rules apply to matters subject by statute to an opportunity for a formal evidentiary public hearing or to matters for which the Commissioner concludes that it is in the public interest to hold a hearing before a Public Board of Inquiry.[212]) The informal hearing procedures are, however, generally subject to a less detailed system of separation of functions. First, the presiding officer in a regulatory hearing required by the act or regulation must "be free from bias or prejudice and may not have participated in the

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[208] 21 C.F.R. § 16.1(a).

[209] *Id.* § 16.1(b).

[210] *Id.* §§ 16.1(b)(2), 202.1(j)(5).

[211] 21 C.F.R. § 16.44(a).

[212] *Id.* § 10.55(a).

investigation or action that is the subject of the hearing or be subordinate to a person, other than the Commissioner, who has participated in such investigation or action.[213] Second, 21 C.F.R. § 16.44, regarding ex parte contacts, provides:

> Those persons who are directly involved in the investigation or presentation of the position of FDA or any party at a regulatory hearing that is required by the act or a regulation should avoid any off-the-record communication on the matter to the presiding officer or the Commissioner or their advisors if the communication is inconsistent with the requirement ... that the administrative record be the exclusive record for decision. If any communication of this type occurs, it is to be reduced to writing and made part of the record, and the other party provided an opportunity to respond.[214]

"[T]he parties to the hearing shall be given reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the action taken or proposed by [FDA] which is the subject of the hearing and a general summary of the information which will be presented by [FDA] at the hearing in support of such action."[215] The parties also "shall have the right to hear a full and complete statement of the action of [FDA] which is the subject of the hearing together with the information and reasons supporting such action."[216] Further, the parties have the right to "conduct reasonable questioning," "to present any oral or written information relevant to such action," to review and correct the required written report of the presiding officer of the hearing, and "to have the hearing transcribed at his expense."[217] This

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[213] 21 U.S.C. § 321(x)(1); 21 C.F.R. § 16.42(b). Nonetheless, neither the Commissioner nor an FDA staff employee to whom the Commissioner may have delegated authority on a matter for which a regulatory hearing is available are precluded by prior participation. *Id.* § 16.42(c)(1). Where there has been prior participation, the Commissioner or the delegate should, if feasible, designate a presiding officer for the hearing who is not a subordinate. *Id.*

[214] *Id.* § 16.44(b).

[215] 21 U.S.C. § 321(x)(3).

[216] *Id.* § 321(x)(4).

[217] *Id.* § 321(x)(4), (5), (6).

procedure puts minimum safeguards in place to ensure that the decisionmaker is not unduly influenced by FDA staff members acting as proponents of the agency's position.

FDA adoption of this established administrative mechanism for determining whether certain promotional materials are false or misleading would benefit all affected parties. Allowing drug manufacturers the opportunity to be heard in an informal hearing *before* FDA determines that certain promotional materials are false and misleading would significantly strengthen the constitutional due process protections afforded to manufacturers.[218] Similarly, requiring such a decision to be supported by record evidence would enhance the integrity of FDA's regime by creating a factual record on which the agency could rely in court and otherwise. Thus, Pfizer strongly recommends that FDA apply these procedures when making determinations as to whether a particular promotional message is false or misleading.

b. Prong 2: Substantial government interest

If FDA cannot establish that the restrained speech is false or misleading or concerns unlawful activity, it alternatively "must demonstrate that the harms it recites are real."[219] The analysis "must identify with care the interests the State itself asserts" and cannot "supplant the precise interests put forward by the State with other suppositions."[220] Neither, however, will the Court "turn away if it appears that the stated interests are not the actual interests served by the

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[218] For example, Allergan has recently stated that it intends to dispute FDA's finding that certain promotional claims concerning Botox Cosmetic wrinkle injections were misleading. Currently, Allergan's only procedural mechanism for reversing FDA short of successfully defending the ad in a court proceeding is for the company to write a response letter to the agency, which "[a]n FDA spokesman" said the agency would "carefully evaluate." *See* Chris Adams, *FDA Calls Botox Claims Misleading*, Wall St. J., Sept. 10, 2002, at D3.

[219] *Edenfield,* 507 U.S. at 770-71.

[220] *Id.* at 768.

restriction."[221] The agency therefore must make clear which of the regulatory interests it seeks to advance provides the basis for any specific action.

c. Prong 3: Direct advancement

The Court also requires FDA to demonstrate that any restrictions on drug manufacturers' commercial speech "will *in fact* alleviate [the asserted harm] to a material degree."[222] For the agency, this constitutional requirement plainly changes the more deferential environment in which its regulatory structure arose. Mere assertion of laudable public health goals is no longer sufficient to justify FDA restraints on truthful, non-misleading speech. Rather, the agency must muster some facts to support the need for employing such restrictions: "A regulation cannot be sustained if it provides only ineffective or remote support for the government's purpose or if there is little chance that the restriction will advance the State's goal."[223] FDA must establish a direct and material link between alleviation of the harm it seeks to prevent and its speech restraint. In the drug information marketplace, where many unregulated speakers communicate information in addition to the regulated manufacturers, the agency is likely to have difficulty satisfying this prong for several restrictions – because despite FDA's control over one class of speakers, the listeners nonetheless will be exposed to the messages from other speakers that the agency may disfavor.[224]

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[221] *Id.*

[222] *Id.* at 770-71 (emphasis added); *accord Rubin*, 514 U.S. at 486-87; *Ibanez*, 512 U.S. at 143.

[223] *Lorillard*, 533 U.S. at 566 (internal quotations and citations omitted). The Court, however, does not "require that empirical data come . . . accompanied by a surfeit of background information . . . . [W]e have permitted litigants to justify speech restrictions by reference to studies and anecdotes pertaining to different locales altogether, or even, in a case applying strict scrutiny, to justify restrictions based solely on history, consensus, and simple common sense." *Id.* at 555 (quoting *Florida Bar v. Went For It, Inc.*, 515 U.S. 618, 628 (1995)) (internal quotations and citations omitted) (alterations in original).

[224] *Cf. WLF*, 13 F. Supp. 2d at 70 ("[T]he FDA does not question a physician's evaluative skills when an article about an off-label use appears among a group of articles in the New England Journal of Medicine, or when one

d. Prong 4: Narrow tailoring between governmental interest and speech restriction

The final prong of the commercial speech analysis requires that FDA "narrowly tailor" its restraints on drug manufacturer advertising and other promotional speech so that the regulations are "not more extensive than is necessary to serve" its legitimate goals.[225] The Court has explained that this means that a regulator must "carefully calculat[e] the costs and benefits associated with the burden on speech imposed" by the regulation at issue.[226] While the fit between the end and means need not be "perfect,"[227] a demonstrable degree of precision is required.[228] Courts will evaluate that precision by considering the availability of other regulatory alternatives:

> A regulation need not be "absolutely the least severe that will achieve the desired end," but if there are numerous and obvious less-burdensome alternatives to the restriction on commercial speech, that is certainly a relevant consideration in determining whether the "fit" between ends and means is reasonable.[229]

FDA recently foundered on this prong in *Western States*. In striking down a statutory prohibition on pharmacist advertisements concerning particular "compounded" drugs, the Court

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physician refers a peer physician to a published article he recently perused, or even when a physician requests a reprint from a manufacturer.").

[225] *See Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410, 434 (1993); *Edenfield*, 507 U.S. at 767; *Fox*, 492 U.S. at 475, *Cent. Hudson*, 447 U.S. at 566.

[226] *Discovery Network, Inc.*, 507 U.S. at 417; *accord Lorillard*, 533 U.S. at 562 (rejecting expansive tobacco advertising regulations on grounds that they "do not demonstrate a careful calculation of the speech interests involved").

[227] *Bd. of Trs. of the State Univ. of N.Y. v. Fox*, 492 U.S. 469, 477 (1989).

[228] Arguably, the Court has interpreted this prong more strictly in the last decade than it did in earlier cases. *Compare Fox*, 492 U.S. at 476-81 *with Thompson v. W. States Med. Ctr.*, 122 S. Ct. 1497, 1506-07 (2002).

[229] *Discovery Network, Inc.*, 507 U.S. at 418 n.13 (citation omitted); *see also, e.g., Rubin*, 514 U.S. at 490-91 (invalidating regulation prohibiting disclosure of alcohol content on beer labeling because temperance goal could be served by, *e.g.*, directly limiting the alcohol content of beer or banning only the emphasis on high alcohol content in advertising).

held that "the Government ha[d] failed to demonstrate that the speech restrictions are not more extensive than is necessary to serve [its asserted] interests."[230] Justice O'Connor's opinion for the majority pointedly noted that earlier Court opinions addressing the fourth prong had made clear that "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so."[231] Yet the legislative record contained "no hint that the Government even considered ... alternatives" to its outright ban on speech."[232] In language phrased to attract attention, the Court declared that "[i]f the First Amendment means anything, it means that regulating speech must be a last – not first – resort. Yet here it seems to have been the first strategy the Government thought to try."[233]

Courts likely will pay particular heed to this language in any future challenges to FDA restraints on commercial speech. Indeed, they have followed this reasoning in invalidating the agency's speech restrictions even before *Western States*.[234] Thus, FDA must seriously consider employing less speech-restrictive alternatives to advance its valid objectives. Moreover, when the agency's concern centers on the potential that the commercial speech at issue may be misleading, FDA will be hard-pressed to show why it cannot rely on disclaimers and other disclosures to cure the purported defect.

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In sum, now that the decision in *Western States* has removed all doubt that FDA's actions are subject to First Amendment scrutiny, the agency must reevaluate its approach to controlling

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[230] *W. States,* 122 S. Ct. at 1506 (internal quotations omitted).

[231] *Id.*

[232] *Id.* at 1506-07 (internal quotations omitted).

[233] *Id.* at 1507.

[234] *See Pearson*, 164 F.3d at 655; *WLF,* 13 F. Supp. 2d at 74.

the flow of information regulated pharmaceutical manufacturers. To accomplish the objective of ensuring that its rules and policies are constitutionally defensible, the agency must closely examine the degree of the restraint in place, the specific interests being advanced, the links between the restraints and the objectives, and the potential for relying on disclaimers and direct conduct incentives as alternatives to speech restrictions. Pfizer now turns to that specific examination.

III. A VIABLE CONSTITUTIONAL APPROACH FOR FDA SPEECH REGULATION

The extensive discussion below is designed to provide FDA with a thorough, rigorous legal analysis of the agency's authority to regulate prescription drug manufacturer speech. This analysis is intended to equip the agency to prepare to defend its regime against First Amendment challenges that may arise in the future. As the discussion below explains, at certain points in the FDA regulatory process, a successful legal defense should simply require a sophisticated application of the relevant law. In other instances, Pfizer recommends that the agency modify its rules and policies to better conform to constitutional requirements.

Pfizer does not intend to suggest, however, that its legal analysis necessarily resolves all policy issues or establishes a complete set of "best practices" with respect to pharmaceutical industry communications about prescription drugs. To the contrary, the discussion below also points out that FDA's ability to provide useful leadership in this regard is not unduly hampered by the Constitution. In those areas where the First Amendment constrains the agency from imposing sweeping, categorical speech rules, FDA remains free to exhort the industry to shape its messages in ways that the government considers to best serve the public health—and to encourage regulated entities to follow the agency's preferred course by providing various incentives, including "safe harbors" against later enforcement or liability actions.

Turning to the questions posed in the Request, Pfizer maintains that the issues raised there are properly separated into two distinct legal analyses. FDA's core gatekeeper role is to review and approve the introduction of new drugs into the marketplace to ensure that they are safe and effective for their intended uses. For FDA to fulfill its important public health mission, it must have the ability to:

(1) determine whether a product is properly classified as a drug and, therefore, within FDA's regulatory authority;

(2) assess whether the product is safe and effective for the uses for which it will be marketed; and

(3) ensure that the product is accompanied by accurate and complete directions to enable physicians to prescribe, and patients to use, the product safely and effectively.

These essential regulatory activities, while requiring FDA to scrutinize the words manufacturers use in describing the uses to which their product may be put, serve the fundamental public health interest in keeping harmful and ineffective products off the market and enabling physicians to prescribe beneficial products safely and effectively. Consequently, any incidental burdens upon speech that might be imposed by the agency's core mission of controlling market access for prescription drugs are appropriately analyzed under a somewhat relaxed standard.

By contrast, once FDA has approved a drug for a particular use and ensured that the key instructional information accompanying the product is sufficient to ensure safe and effective use, the agency's regulatory authority over manufacturers' speech relates to market integrity – and therefore is far more constitutionally circumscribed. This two-tiered constitutional framework for analyzing FDA's regulation of speech strikes an appropriate balance between (1) protecting FDA's ability to safeguard the public health by limiting market access to drugs that are safe and

effective and can be so used, and (2) upholding manufacturers' constitutional rights to engage in truthful and nonmisleading speech about their products.

For analytic clarity, Pfizer identifies the tier in which each of FDA's regulatory activities belongs – but the company employs the same multi-question approach in fleshing out the ramifications of the analysis. First, Pfizer sets forth FDA's current regulatory regime and its enforcement mechanisms. Next, the company analyzes whether the restriction at issue is a restraint on protected speech, whether the speech is constitutionally protected at all, the severity of the speech restraint at issue, whether it is incidental to a regulation of conduct, and the legal standard under which the restriction is appropriately analyzed. Pfizer then examines the interest(s) that the restraint is intended to advance, whether the restriction in fact directly advances that interest, and whether there are more narrowly tailored alternatives by which to advance the same interest. Pfizer concludes each module by recommending changes to FDA's current regime where appropriate.

A. FDA'S AUTHORITY TO REGULATE PRODUCTS AS DRUGS

The foundation for FDA's regulatory jurisdiction over drugs is on the claims that a manufacturer makes regarding a particular product. Although FDA's regime imposes certain consequences on a manufacturer depending on what it says about its products – *e.g.*, the obligation to test its product for safety and effectiveness and seek FDA approval before marketing – as Pfizer demonstrates below, that regime is nonetheless sustainable under the First Amendment.

1. Current Regulatory Regime (Jurisdiction)

FDA's authority to regulate a product as a drug to ensure its safety and effectiveness "depends upon the use of words, such as whether a product is marketed with claims that it can

affect the structure or function of the body of man, or treat disease."[235] For example, an ingredient in "Elixir Sulfanilamide-Massengill" – the product responsible for numerous deaths in the 1930s, which led to the eventual passage of the FDCA in 1938 – was diethylene glycol, a solvent also found in paint, varnish, and anti-freeze.[236] While it is lawful to market that chemical as part of a paint, varnish, or anti-freeze without first obtaining FDA's approval, if the manufacturer markets the chemical as a cure-all wonder drug that treats a variety of ailments (or, for that matter, even a single ailment), FDA has statutory authority to regulate the product as a "drug" under the FDCA.[237] The manufacturer must then demonstrate that the product is safe and effective for the claimed uses before the statute will allow the product to be sold for those purposes.[238]

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[235] *See Request for Comment on First Amendment Issues*, 67 Fed. Reg. 34,942, 34,943 (May 16, 2002) ("Request"); 21 C.F.R. § 201.128; 21 U.S.C. § 321(g)(1) (defining drugs, as, *inter alia,* "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man" or "articles (other than food) intended to affect the structure or any function of the body of man"); *see also* S. Rep. No. 73-493, at 2-3 (1934) ("The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."); *United States v. Nutrition Serv., Inc.*, 227 F. Supp. 375, 386 (W.D. Pa 1964) (characterizing product derived from natural components such as wheat, yeast, salt and water as a drug based on manufacturer claims that it treated cancer and stating that "[t]he real test is how this product is being sold"), *aff'd* 347 F.2d 233 (3d Cir. 1965); *United States v. An Article . . . "Sudden Change,"* 409 F.2d 734, 739 (2d Cir. 1969) (characterizing cosmetic lotion as a drug based on claims that it was equivalent to a face lift without surgery and observing that "[r]egardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims show intended uses that bring it within the drug definition"); *United States v. 354 Bulk Cartons . . . Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847 (D.N.J. 1959) (characterizing cigarettes claiming a weight-control use as drugs). Throughout these comments, Pfizer collectively refers to the types of claims that enable FDA to regulate a product as a drug as "disease claims."

[236] Thomas F. McGuire, *Food, Drug, or Both?: Dual Classification under the Federal Food, Drug, and Cosmetic Act*, 1984 U. Ill. L. Rev. 987, 991-92.

[237] *See* 21 U.S.C. §§ 321(g)(1), 355(c)(1)(A), (d) (requiring FDA to keep off the market drugs that are unsafe and/or ineffective for the conditions of use "prescribed, recommended, or suggested in the proposed labeling thereof"); *see also United States v. Rutherford*, 442 U.S. 544, 549-51 (1979) (regulating substance commonly found in fruit pits as a new drug when substance was claimed to treat cancer).

[238] *See* 21 U.S.C. §§ 331(d), 355(a), (c)(1)(A), (d).

2. Current Enforcement Mechanisms (Jurisdiction)

FDA has a number of enforcement tools that it may use to ensure that only products that are safe and effective for their intended uses are marketed as drugs. If a manufacturer sells or attempts to sell a drug without FDA's approval, FDA may seek a federal injunction to prohibit it from doing so.[239] If the unapproved product is already on the market, FDA may seize it and withdraw it from the market.[240] FDA also may bring criminal proceedings to fine and/or imprison a manufacturer who sells an unapproved drug. For a first offense, the manufacturer "shall be imprisoned for not more than one year or fined not more than $1,000, or both."[241] Subsequent offenses trigger heightened penalties of up to three years in prison and a fine of up to $10,000, or both.[242] Taken together, FDA's extensive arsenal of enforcement weapons ensures that FDA's drug regulations have teeth if the words a manufacturer uses place it in the regulated zone.

3. Is the Restriction a Restraint on Protected Speech? (Jurisdiction)

FDA's jurisdictional basis for regulating products as drugs does not improperly restrain protected speech. Congress has made it unlawful to sell a product for health care purposes without first establishing that the product is safe and effective for that use. As *Pittsburgh Press*[243] and *Wisconsin v. Mitchell*[244] make clear, the First Amendment does not bar FDA from

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[239] *Id.* § 332(a).

[240] *Id.* § 334.

[241] *Id.* § 333(a).

[242] *Id.*

[243] 413 U.S. 376, 389 (1973).

[244] 508 U.S. 476, 489 (1993).

using manufacturer claims to determine whether a product is being shipped for purposes that require prior approval by FDA.

Protected Speech? Where a manufacturer makes disease claims about a product it is selling, its speech characterizes its conduct as the sale of a regulated drug product. FDA approval is then required for interstate shipment. FDA does not purport to regulate the claims that could be made, for example, by an unrelated third party without government approval. Thus, any impact on speech is incidental to shipment regulation.

Moreover, unverified claims of health benefits may promote shipments that produce substantial harms to consumers, who may be injured or even killed by taking unsafe products represented to treat various ailments. Thus, even if FDA were deemed to be restricting the claims themselves, "'[p]otentially expressive activities that produce special harms distinct from their communicative impact ... are entitled to no constitutional protection.'"[245]

Severity of Restraint: The FDCA prohibits a manufacturer from shipping a product about which it makes disease claims until FDA has reviewed the claims and determined that the product is safe and effective for those uses. Because FDA's review of that speech implicates no First Amendment protections, however, the usual strong presumption against the constitutionality of prior restraints does not come into play.[246]

Speech Restriction Incidental to Conduct? FDA's drug regulations prohibit the unlawful introduction into interstate commerce of unapproved drugs; they do not suppress manufacturer speech about their products per se. Rather, a manufacturer remains free to make disease claims about its products so long as it does not sell them. It is true that a manufacturer

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[245] *Mitchell*, 508 U.S. at 484 (citing *Roberts v United States Jaycees*, 468 U.S. 609, 628 (1984) (alterations in original)).

[246] *See supra* Part II.B at 41-42.

may be deterred from making drug claims about a product that will trigger FDA's assertion of jurisdiction and prevent the manufacturer from selling the product for those claimed uses until FDA has approved marketing it for those uses. Nevertheless, any such restraint on speech is ancillary, or incidental, to FDA's central goal of preventing a product's entry into the health-care market without prior approval.

Relevant Legal Standard: Because the First Amendment does not foreclose FDA's focus on manufacturer claims, FDA's jurisdictional basis for regulating products as drugs is subject only to the deferential rational basis test as set forth in *Carolene Products*,[247] which raises no obstacle to FDA in barring unapproved products from the market.

4. What Substantial, Legitimate Interest Does the Restraint Serve? (Jurisdiction)

Of all FDA's interests in regulating products about which the manufacturer makes drug claims, the gatekeeper concern – *i.e.*, the agency's interest in ensuring that only demonstrably safe and effective drugs enter the U.S. marketplace – is most compelling. Indeed, one need look no further than the tragic historical example of Elixir Sulfanilamide-Massengill discussed above to conclude that the agency has a compelling interest in regulating products marketed for uses that purport to affect the human body. FDA's effective ability to regulate in such instances may be, quite literally, a matter of life and death.[248]

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[247] *See Carolene Prods.*, 304 U.S. at 152; *supra* Part II.C.2, at 50.

[248] *See, e.g., Thompson v. W. States Med. Ctr.*, 122 S. Ct. 1497, 1505 (2002) (recognizing importance of governmental public health interest in safeguarding new drug approval process); *Lorillard*, 533 U.S. at 555 (recognizing "importance of the State's interest in preventing the use of tobacco products by minors"); *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 485 (1995) ("[T]he Government here has a significant interest in protecting the health, safety, and welfare of its citizens ...."); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998) ("*WLF*") (acknowledging substantiality of FDA's "interest in protecting the health and safety of its citizens"), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

5. Does the Restraint Directly Advance a Legitimate Interest? (Jurisdiction)

Prohibiting a manufacturer from selling a potentially harmful product for human health uses until it has been precleared for safety and effectiveness for those uses is the most direct way for FDA to protect consumers from unsafe and/or ineffective treatments. If the untested product is not in the health market at all, it cannot harm consumers.

6. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Jurisdiction)

The agency cannot effectively determine whether a product will be shipped and promoted as a drug based on the chemistry of the substance alone – it must know the uses for which the product will be marketed. As the Elixir Sulfanilamide-Massengill example illustrates, a chemical can be sold for a variety of purposes: diethylene glycol may appropriately be sold as part of a paint, varnish, or antifreeze, but cannot safely be sold as a cure-all therapy.

Although Congress could conceivably instruct the FDA to examine the actual use to which products are put, this is a less direct and effective way of gauging whether a product will be used as a drug. Moreover, because that analysis occurs after the product has been used, it risks that many consumers will be harmed by unsafe products before FDA determines that they are being used as drugs.

In short, it is difficult to imagine a more targeted means by which FDA can identify a product as a proper subject of drug regulation than by examining the manufacturer's express claims.

7. Recommended Rule and/or Policy Change (Jurisdiction)

FDA's existing claims-based jurisdictional focus is the most effective and narrowly tailored way for the agency to ascertain whether a manufacturer seeks to enter the health care business. Therefore, Pfizer recommends no changes to FDA's regime for asserting jurisdiction.

B. FDA'S AUTHORITY TO PRECLEAR PRESCRIPTION DRUGS AND THEIR OPERATIVE LABELING BEFORE MARKETING

Just as FDA cannot determine whether it may regulate a product as a drug without examining what the manufacturer says about the product, neither can it ensure that the product is safe and effective, and includes accurate and complete instructions for using the product safely and effectively, without looking at the product's professional labeling concerning how, and for what, the product is to be used. The FDCA defines "labeling" to include "written, printed, or graphic matter upon . . . or accompanying [the drug]."[249] FDA, however, has more broadly defined the term to include a variety of materials that do not physically accompany the drug but that do "contain[] drug information" and are supplied by or on behalf of the manufacturer, packer, or distributor "for use by medical practitioners, pharmacists, or nurses."[250] With respect to prescription drug labeling that in particular "furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug," FDA requires the "labeling," *inter alia*:

- to "contain a summary of the essential scientific information needed for the safe and effective use of the drug";
- to "be informative and accurate and neither promotional in tone nor false or misleading in any particular"; and
- to comply with a number of highly specific content and format requirements.[251]

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[249] 21 U.S.C. § 321(m).

[250] 21 C.F.R. § 202.1(l)(2) (defining labeling to include "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published ... for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor").

[251] *Id.* §§ 201.100(d), 201.56(a), (b), 201.57.

Pfizer limits its analysis of FDA's ability to regulate "labeling" to prescription drug labeling that purports to serve the above purpose for physicians, contains the above information, and complies with the specified requirements. This is, for the most part, the physician package insert, which is reprinted in the PDR. Pfizer refers to that labeling as "operative labeling" because Pfizer believes that it is the only appropriate labeling upon which health care professionals should rely to ascertain the operative instructions for use of a drug. Indeed, some sources indicate that it is the information physicians turn to the most when prescribing medications. The vendor of the PDR, for example, asserts that the book "is considered the standard prescription drug reference and can be found in virtually every physician's office, hospital and pharmacy in the United States" and that "nine out of ten doctors consider PDR their most important reference source."[252] The operative labeling constitutes an inherent part of the drug itself and contains dosage and use instructions, warnings, contraindications, and other valuable information that enable doctors to prescribe the product safely and effectively.

Pfizer believes that FDA does a disservice to the health care community in characterizing other types of materials such as calendars, sound recordings, and the like as prescription drug "labeling."[253] FDA's characterization incorrectly suggests that these materials are appropriate substitutes for the operative instructions for use found on a drug's package insert in ascertaining the safe and effective administration of a drug. For this reason, Pfizer analyzes other types of materials beyond the operative labeling – such as information appearing in brochures, calendars, books, or handouts from manufacturers or detail persons – as "advertising," a term that Pfizer

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[252] *See* Thomson's Promotional Literature for 2003 PDR, available at <http://www.medecbookstore.com/Merchant2/merchant.mv?Screen=PROD&Store_Code=001&Product_Code=PDR3P&Category_Code=pdr>; *see also* Proposed Labeling Requirements, 65 Fed. Reg. 81082, 81083 (Dec. 22, 2000), *citing* National Biosystems, Inc., *Focus Group Report: Physicians' Perceptions of Prescription Drug Labeling Information* at 3 (1992) (identifying PDR as physician participants' most common source for drug information).

[253] *See* 21 C.F.R. § 202.1(l)(2).

uses to denote material designed to "attract public attention or patronage."[254] Pfizer encourages FDA to narrow its definition of "labeling" to refer only to the operative labeling as Pfizer has defined that term.

Well-settled Supreme Court and other judicial precedent confirms that Pfizer's targeted, functional approach to the concept of labeling is correct. In *Kordel v. United States*,[255] the Supreme Court made clear that where material "performs the function of labeling," it should be treated as such.[256] The Court narrowly described that function as follows:

> In this case the drugs and the literature had a common origin and a common destination. The literature was used in the sale of the drugs. It explained their uses. *Nowhere else was the purchaser advised how to use them.* It constituted an *essential supplement to the label attached to the package.* Thus the products and the literature were interdependent ....[257]

As the above passage demonstrates, the Supreme Court regarded as labeling material that did not merely explain a drug's uses but constituted "essential" – indeed, the only – information received by the purchaser on drug usage that was inextricably linked with the product itself. The United States Court of Appeals for the Second Circuit subsequently confirmed this functional definition of labeling: "There is a line to be drawn, and, if the statutory purpose is to be served, it must be drawn in terms of the function served by the writing."[258] FDA should conform its

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[254] *Webster's II New College Dictionary* 17 (2001). FDA defined "advertising" in the various bills leading up to the 1938 Act as representations disseminated to the public in any manner or by any means other than by the labeling for the purposes of inducing, directly or indirectly, the purchase of food, drugs, devices, or cosmetics. *See* S. 1944, 73d Cong. § 2(j) (1933); S. 2000, 73d Cong. § 2(j) (1934); S. 2800, 73d Cong. § 2(j) (1934); S. 5, 75th Cong. § 201(j) (1935); S. 5, 75th Cong. § 2(o) (1937). There is, however, no definition of advertising in the Act.

[255] 335 U.S. 345, 348 (1948).

[256] *Id.* at 350. The Court rejected the view that "labeling" necessarily must physically accompany a drug during shipment into interstate commerce in favor of the more functional approach discussed in the text. *Id.*

[257] *Id.* at 348 (emphasis added).

[258] *United States v. 24 Bottles*, 338 F.2d 157, 158-59 (2d Cir. 1964).

definition of "labeling" with the teaching of these cases by carefully considering the purpose served by various materials before concluding that they should fall within that definition.

* * *

FDA regulates both the substantive content and the format of prescription drug labeling. In addition, FDA sometimes regulates the particular nonsubstantive manner of expression in which manufacturers comply with FDA's substantive requirements – *e.g.*, the precise wording for describing pharmacology, contraindications, or warnings. Because the substantiality of both FDA's interest in regulating and the manufacturer's interest in expressing itself in each of these areas varies, Pfizer analyzes them separately below.[259]

1. FDA's Ability To Regulate Labeling Substance

a. Current Regulatory Regime (Labeling Substance)

Pursuant to the FDCA, FDA requires a manufacturer of a new drug to preclear its operative labeling with FDA before the drug is approved for marketing.[260] A manufacturer must also preclear changes to its operative labeling after approval with FDA unless the change will:

- "add or strengthen a contraindication, warning, precaution, or adverse reaction";
- "add or strengthen a statement about drug abuse, dependence, or overdosage";
- "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product"; or
- "delete false, misleading, or unsupported indications for use or claims for effectiveness."[261]

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[259] For each of the categories, Pfizer assumes that the regulations are within the constitutional power of government pursuant to the Interstate Commerce Clause and therefore meet the first prong of the *O'Brien* test. *United States v. O'Brien*, 391 U.S. 367, 377 (1968). Pfizer is not addressing any possible issues of statutory authority.

[260] 21 U.S.C. § 355(b)(1)(F).

[261] 21 C.F.R. § 314.70(c)(2).

Even in these cases, the manufacturer still must notify FDA of the change in a supplemental application, and FDA still has the power to approve or deny the changes.[262]

FDA's current regulations require manufacturers to include in prescription drug labeling a variety of information concerning the drug, including, *inter alia*, indications and usage, dosage and administration, contraindications, warnings, adverse reactions, and overdosage information.[263] Within the past two years, FDA has proposed modifying these regulations to require the inclusion of additional substantive information.[264]

b. Current Enforcement Mechanisms (Labeling Substance)

FDA has a number of authorities and enforcement tools that it may use to ensure that only drugs with proper operative labeling are marketed. First, the FDCA gives FDA prior approval authority over drugs, pursuant to which a manufacturer must establish that the operative labeling of its drugs is truthful and not misleading before FDA will permit the drug to be sold.[265] The FDCA also gives FDA misbranding authority to prevent manufacturers from selling drugs with false or misleading labeling.[266] FDA may enforce its pre-approval and misbranding

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[262] *See id.* § 314.70(a) (requiring applicant to submit supplemental application for most post-approval labeling changes); *id.* § 314.71 (applying all NDA procedures and actions under Part 314 to supplements), *id.* § 314.125 (providing that application may be denied if, *inter alia*, "proposed labeling does not comply with the requirements for labels and labeling in part 201").

[263] *See id.* §§ 201.56, 201.57.

[264] *See* Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics: Requirement for Prescription Drug Product Labels, 65 Fed. Reg. 81,082, 81,112-23 (proposed Dec. 22, 2000) ("Proposed Labeling Requirements").

[265] 21 U.S.C. § 355(d)(7).

[266] *Id.* § 352(a) (declaring drug to be misbranded "[i]f its labeling is false or misleading in any particular"); *id.* § 331(a) (prohibiting sale of misbranded drugs); *id.* § 331(b) (prohibiting misbranding of marketed drug); *id.* § 331(c) (prohibiting receipt in interstate commerce of misbranded drug).

authorities through the tools of injunction, seizure, criminal fines, and imprisonment discussed above.[267]

c. Is the Restriction a Restraint on Protected Speech? (Labeling Substance)

FDA's substantive regulations of operative labeling constitute only an incidental restraint on protected speech. As explained below, FDA's prior approval of the operative instructions for using a product is an element of FDA's determination that drugs, when introduced into interstate commerce, can be safely and effectively used for their intended purposes; any burden on speech is ancillary to FDA's regulation of manufacturers' conduct in shipping drugs into interstate commerce. Thus, Pfizer believes that the constitutionality of these regulations would be analyzed under the *O'Brien* test.[268]

Protected Speech? The substantive information that appears on a drug's operative labeling does not concern unlawful activity – the drug will not be on the market until the labeling is approved. Nor does the speech fall into any other category of expression that is exempt from the First Amendment's guarantees. Thus, the speech is constitutionally protected.

Severity of Restraint: FDA's requirement that a manufacturer preclear its operative labeling and most changes thereto is a classic prior restraint on speech. Although generally such prior restraints must be analyzed with a skeptical eye,[269] the integration of FDA's speech with its substantive review justifies the prior restraint.

Speech Restriction Incidental to Conduct Regulation? FDA's substantive regulations of a drug's operative labeling do not aim to suppress manufacturer speech. Rather, they are one

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[267] *See supra* Part III.A, at 67.

[268] *See O'Brien*, 391 U.S. at 377.

[269] *See supra* Part II.B, at 41-42.

part of FDA's overall regulatory framework – which also includes testing requirements and manufacturing process provisions, among other regulations – to ensure safe and effective drug use by barring market access to unproven, unsafe, and/or ineffective drugs. As FDA recently has stated, "the evaluation of a drug's safety and effectiveness is thus inextricably intertwined with its labeling."[270] The professional labeling regulations are part and parcel of, and only incidental to, the valid regulation of noncommunicative conduct – *i.e.*, the introduction of drugs into interstate commerce – and pose only an incidental burden on speech at most.

Relevant Legal Standard: Pfizer believes that the constitutionality of FDA's incidental restrictions on a manufacturer's operative labeling should be analyzed under the flexible *O'Brien* test, which holds that only "a sufficiently important governmental interest in regulating the nonspeech element can justify incidental limitations on First Amendment freedoms."[271]

If FDA's operative labeling restrictions are instead found to be restrictions of speech per se, they would be analyzed under the strict scrutiny test applicable to fully protected speech.[272] As shown below, however, regardless of which test applies, FDA's regulations are constitutionally sustainable.

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[270] Amicus Brief for the United States in Support of the Defendant-Appellee and Cross-Appellant, and in Favor of Reversal of the District Court's Order Denying Partial Summary Judgment to Defendant-Appellee and Cross-Appellant, *Motus v. Pfizer Inc.* at 5 (9th Cir. Sept. 3, 2002) (No. 02-55498).

[271] *O'Brien*, 391 U.S. at 376. Because FDA explicitly requires that prescription drug labeling be nonpromotional in nature and because the labeling details how to use a product, rather than proposing a commercial transaction, professional labeling does not constitute commercial speech, and the *Central Hudson* analysis therefore does not apply. *See* 21 C.F.R. § 201.56(b); *see also* Proposed Labeling Requirements, 65 Fed. Reg. at 81084 (stating that "labeling ... is consulted *after* the physician has made a tentative prescribing decision") (emphasis added) ("Proposed Labeling Requirements").

[272] *See supra* Part II.B, at 48-49; *United States v. Playboy Entertainment Group, Inc.*, 529 U.S. 803, 813 (2000) (characterizing "strict scrutiny" test as requiring speech-restrictive regulations to be "narrowly tailored to promote a compelling Government interest" and the least restrictive means of achieving that interest).

d. What Substantial, Legitimate Interest Does the Restraint Serve? (Labeling Substance)

"There are few, if any, more important functions performed by any regulatory agency than ... ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it."[273] FDA's operative labeling regulations serve this all-important public health interest by ensuring that drugs are safely and effectively used for their intended purposes. Because "the right dose differentiates a poison and a remedy,"[274] whether a product is safe or effective hinges upon what the product is used to treat and the manner in which it is used, including the dosage, frequency of administration, route of administration, etc., it is impossible to make this crucial assessment without such information. For the agency to achieve its overall goal of ensuring that only safe and effective drugs are marketed, it is essential that FDA have the ability to assess both the product itself and the operative words delineating precisely how that product is to be used.

e. Does the Restraint Directly Advance a Legitimate Interest? (Labeling Substance)

FDA's extensive substantive operative labeling regulations directly advance the agency's interest in ensuring that products are safely and effectively used. Indeed, the most direct way to ensure that doctors appropriately prescribe drugs and instruct their patients on safe and effective use is to require that they be informed of important information concerning indications, dosage,

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[273] *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998) ("*WLF*"), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

[274] Michael A. Gallo, *History and Scope of Toxicology, in Casarett and Doull's Toxicology: The Basic Science of Poisons* 1, 4 (Curtis D. Klaassen, 5th ed. 1996) (quoting Paracelsus) (*cited in* Mark Landy & Kyle D. Dell, *The Failure of Risk Reform Legislation in the 104th Congress,* 9 Duke Envtl. L. & Pol'y F. 113, 130 n.80 (1998)); *see also United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk.").

pharmacology warnings, contraindications, side effects, and the like, a function that FDA's regulations perform.

f. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Labeling Substance)

There is no other way to communicate important drug use information and warnings to professionals except through words, and the best place for those words to appear is on the information source to which doctors most logically turn to learn this essential information – the drug's operative labeling.[275] FDA must have the ability to regulate the substance of this information in advance of its dissemination so that physicians have the information to prescribe drugs in a way that will prevent consumers from being harmed, or even killed, due to inadequate or incorrect information. There simply is no more equally targeted, less speech-restrictive way for FDA to achieve this important goal.

Moreover, FDA's operative labeling regulations do not suppress speech but require the disclosure of extensive information that a manufacturer might not otherwise provide on the label. A manufacturer remains constitutionally free to speak about approved uses of his or her product in a truthful and nonmisleading manner in a number of other contexts, discussed in Sections III.D and III.E below.

g. Recommended Rule and/or Policy Change (Labeling Substance)

FDA's operative labeling regulations constitute the most direct, targeted way for FDA to ensure that doctors have the complete and accurate information that they need to determine the safest and most effective courses of treatment for their patients. Therefore, Pfizer recommends no changes to FDA's existing substantive labeling regulations.

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[275] *See id.*

2. FDA's Ability To Regulate Labeling Format

FDA's ability to regulate labeling format presents a somewhat closer question. FDA must demonstrate that specific labeling format regulations, above and beyond the agency's substantive labeling requirements, directly and materially advance the agency's interest in ensuring that drugs bear complete, accurate, and easy-to-understand operative instructions for use so that doctors administer drugs safely and effectively. In light of the substantial empirical evidence that appears to support use of a single, uniform labeling format across products as enhancing readability, Pfizer believes that FDA could sustain certain reasonable format requirements against a First Amendment challenge.

a. Current Regulatory Regime (Labeling Format)

FDA's current regulations contain a limited number of format requirements, such as the requirement that substantive information appear in a particular order[276] and the requirement that warnings for particular drugs appear in boxes.[277] In December 2000, FDA proposed to impose extensive additional format requirements, including the use of bold-face type for certain text, horizontal lines to separate major sections of the labeling, "bullet points to distinguish multiple subheadings," a minimum font size of 8 points for all labeling text, length restrictions, vertical lines in the margin of modified labeling to indicate changes, "▼" to indicate that the product has been approved less than three years, and "℞" to indicate that the product is a prescription drug.[278]

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[276] *See* 21 C.F.R. § 201.56(d)(1).

[277] *See, e.g., id.* § 201.316 (requiring boxed warning for use with drugs with thyroid hormone activity); *id.* § 210.317 (requiring boxed warning for use with digitalis).

[278] Proposed Labeling Requirements, 65 Fed. Reg. at 81,088, 81,096-97.

b. Current Enforcement Mechanisms (Labeling Format)

As was true for FDA's substantive labeling requirements, FDA has a number of tools – including pre-approval and misbranding authority, enforced through injunction, seizure, criminal fines and imprisonment – that give teeth to its proposed formatting requirements.[279] These tools, however, hinge upon FDA's successful demonstration that formatting noncompliance renders the operative labeling false or misleading, which may be more difficult to establish with respect to formatting than substantive requirements.

Nonetheless, as the agency whose authorizations directly control manufacturers' ability to engage in business, FDA enjoys considerable scope to wield *in terrorem* power over drug makers by threatening to withhold product approval until the manufacturer formats its operative labeling in the manner preferred by FDA. This threat need never be articulated to be effective – because FDA effectively licenses a pharmaceutical manufacturer's current and future product line, the agency need only "regulate by raised eyebrow" to coerce drug makers into complying with FDA's desired outcome. Courts are quite aware that "a regulatory agency may be able to put pressure upon a regulated firm in a number of ways, some more subtle than others."[280]

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[279] *See supra* Part III.A.2, at 67.

[280] *MD/DC/DE Broadcasters Ass'n v. FCC*, 236 F.3d 13, 19 (D.C. Cir. 2000) (noting the possibilities for "a variety of *sub silentio* pressures and 'raised eyebrow' regulation"), *denied en banc*, 253 F.3d 732 (2001), *cert. denied*, 122 S. Ct. 920 (2002); *see also, e.g., Writers Guild of Am., W., Inc. v. Am. Broad. Co.* 609 F.2d 355, 365 (9th Cir. 1979) ("Regulation through 'raised eyebrow' techniques or through forceful jawboning is commonplace in the administrative context, and in some instances may fairly be characterized . . . as official action by the agency.") (footnotes omitted); *Writers Guild of Am.*, 609 F.2d at 365-66 (noting that "the line between permissible regulatory activity and impermissible 'raised eyebrow' harassment of vulnerable licensees is . . . exceedingly vague"); *Consol. Edison Co. v. Fed. Power Comm'n*, 512 F.2d 1332, 1341 (D.C. Cir. 1975) ("Regulation through 'raised eyebrow' techniques seems inherent in the structure of most administrative agencies, combining as they do both policy-making and adjudicative functions.").

c. Is the Restriction a Restraint on Protected Speech? (Labeling Format)

Protected Speech? The manner in which a manufacturer formats the operative labeling for its drugs constitutes expressive activity that does not concern unlawful conduct and is not otherwise exempt from the guarantees of the First Amendment.[281] Thus, the First Amendment protects that form of expression.

Severity of Restraint: FDA's requirement that a manufacturer preclear the format of its operative labeling operates as a prior restraint on speech, triggering a presumption against the constitutionality of such a regulation.[282]

Speech Restriction Incidental to Conduct Regulation? FDA's regulations are not directed to the suppression of information and instead aim at providing a uniform format to enhance the readability of essential drug information, and thereby the safety and effectiveness of the drug. As is true for FDA's substantive requirements, FDA's formatting restrictions are only one incidental component of its overall scheme to ensure that drugs are safe and effective and safely and effectively used.

Moreover, FDA attempts to preserve substantial flexibility for manufacturers in the communicative element of those requirements, suggesting in its Proposed Labeling Requirements to allow manufacturers, for example, to select the particular bullet character of their choice and to select any font size for labeling statements of 8 points or larger rather than dictating the specific font size in which labeling must appear.[283] As such, FDA's proposed formatting regulations do not appear materially to inhibit manufacturers' free expression of the

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[281] *See supra* Part II.C, at 49-50.

[282] *See supra* Part II.B, at 41-42.

[283] *See* Proposed Labeling Requirements, 65 Fed. Reg. at 81,096.

required substantive information but merely enable physicians quickly to obtain a grasp of the important drug information that they need, as discussed below. They are, in effect, akin to a time, place or manner regulation of speech for non-content purposes.

Relevant Legal Standard: Because FDA's formatting restrictions are only a small part of FDA's overall regulatory regime aimed at regulating drug sales, not speech per se, and their burden on speech is incidental and minimal, Pfizer believes that their constitutionality is appropriately analyzed under the lenient *O'Brien* level of scrutiny.[284]

d. What Substantial, Legitimate Interest Does the Restraint Serve? (Labeling Format)

In the preamble to FDA's proposed formatting revisions, the justification FDA expressed for its proposals was that "typically lengthy and undifferentiated format of prescription drug labeling makes it difficult to locate and read specific information" and that "new minimum standards and requirements for the format of prescription drug labeling [would] improve its legibility, readability, and usability."[285] Thus, FDA's proposed formatting standards further FDA's substantial interest in ensuring the safe and effective use of prescription drugs by making important usage and warning information easily and quickly ascertainable. This improved readability is particularly important in a world where doctors spend less and less time on average with their patients and where they therefore need to have essential prescribing information at the tip of their fingers. Doctors can more readily compare the suitability of different medications for a patient if the indications, drug interactions, warnings, etc., appear in the same place in the respective listings on the operative labeling of various drugs.

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[284] *See supra* Part II.B, at 51-52 (discussing *O'Brien*, 391 U.S. at 377).

[285] Proposed Labeling Requirements, 65 Fed. Reg. at 81,096.

e. Does the Restraint Directly Advance a Legitimate Interest? (Labeling Format)

Numerous studies demonstrate that presenting information concerning a particular product in a uniform manner across all products in that class enables readers more easily to digest that information and find particular pieces of that information most relevant to them.[286] Moreover, FDA in its proposed prescription drug labeling rulemaking cited to a number of studies and articles suggesting that certain formatting requirements enhance readability, thereby enabling physicians more efficiently to ascertain the safe and effective use of a product.[287]

Other contexts where standardized formats are used likewise demonstrate that uniform layout materially and directly furthers FDA's goal of providing easily accessible, readable drug use information. FDA's standardized format for nutritional information on food labels[288] has been successful and widely praised.[289] Other governmental and private groups have similarly

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[286] *See, e.g.* Michael J. Kalsher et al., *Enhancing the Perceived Readability of Pharmaceutical Container Labels and Warnings: The Use of Alternative Designs and Pictorials*, Proceedings of the Human Factors and Ergonomics Society 38th Annual Meeting (1994) (lack of standardization in label formatting and content results in problems in reading and understanding warnings); David R. Desaulnier, *Layout, Organization, and the Effectiveness of Consumer Product Warnings*, Human Factors Prospectives on Warnings 38 (Kenneth R. Laughery et al. eds., 1994) (comprehension increases when information is placed in predictable units).

[287] *See, e.g.*, 65 Fed. Reg. at 81,112. For sources supporting specific requirements proposed in FDA's Proposed Labeling Rulemaking, see National BioSystems, Inc., *Focus Group Report: Physicians' Perceptions of Prescription Drug Labeling Information* (1992) (highlighting important information and increasing the type size, *inter alia*, enhance physicians' perceptions of labeling information); A.J. Wilkins & M.I Nimmo-Smith, *The Clarity and Comfort of Printed Text*, 30 Ergonomics 1705-20 (1987) (bold type increases comprehension of warnings); Miles A. Tinker, Legibility of Print 67-73, 88-107 (1963) (font size is an important factor in determining legibility and reading time); Steering Committee for the Collaborative Development of a Long-Range Action Plan for the Provision of Useful Prescription Medicine Information, *Action Plan for the Provision of Useful Prescription Medicine Information* 16-25, 57-58 (1996) (pictograms and summary sections are useful tools for increasing comprehension); Macro International, Inc., *Women's Health Study Focus Groups Report* (1996) (participants in focus group wanted drug labeling to include, *inter alia*, indication of length of time a product has been on the market).

[288] *See* Nutrition Labeling and Education Act of 1990 (NLEA), Section 403 of the FDCA.

[289] *See* FDA Commissioner Jane E. Henney, M.D., Keynote Address at the Annual Executive Conference (1999) ("We hope the new OTC label will be as widely praised as the NLEA food label has been to help consumers make healthy choices"), *quoted in* Consumer Healthcare Products Ass'n, *Executive Newsletter,* 6-99, at 8 (Mar. 19, 1999), *available at*: http://www.chpa-info.org/pdfs/03-19%20XNL.pdf.

perceived the benefits of presenting information in a uniform format. The FTC, for example, requires a standard format for the mandatory "EnergyGuide" label, which reports energy efficiency for a variety of appliances.[290] Thus, it is beyond serious question that FDA's requirement that important operative labeling information be presented in standardized form directly advances FDA's interest in ensuring that physicians are able to prescribe, and patients are able to take, drugs safely and effectively.

f. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Labeling Format)

While there may be a number of formats that would work equally well to accomplish FDA's goal of enhancing operative labeling readability, and therefore usefulness, there is a substantial benefit in employing a single, uniform format, irrespective of the specific parameters of the chosen format, to achieve this end. That way, doctors can become accustomed to a single, uniform format instead of having to search for the same information appearing in different places on the operative labeling for different drugs. There is no non-speech alternative for advancing FDA's substantial interest in making information on the operative labeling more understandable than by conforming it to a standardized format. There may, however, be alternative formatting requirements that are less burdensome to manufacturer speech than those that FDA ultimately selects. FDA should take care to ensure that the formatting requirements that it imposes are, in fact, reasonable and one of the least speech-restrictive formatting alternatives that will effectively further its interest in guaranteeing easily readable operative labeling.

g. Recommended Rule and/or Policy Change (Labeling Format)

In light of the foregoing, it is reasonable and constitutionally acceptable for FDA to select, within reason, a single useful format to which manufacturers must conform to advance

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[290] *See* 10 C.F.R. pt. 430.

this important goal. Pfizer therefore recommends no changes to FDA's current and proposed formatting requirements provided that FDA's proposed requirements become no more onerous or extensive than they currently are. Because there is the potential for FDA oversight in this area to become more than a mere "incidental burden" on speech, thereby burdening speech more than is necessary, FDA must tread carefully in this area.[291]

3. FDA's Ability To Regulate the Manufacturer's Nonsubstantive Manner of Expressing the Required Substance

FDA's constitutional case is weakest when it attempts to dictate the specific wording that a manufacturer chooses in conveying the required substantive information. While it is squarely within FDA's mandate to require manufacturers to convey certain safety and use-related messages concerning the drugs they sell, the First Amendment does not permit the agency to dictate the precise words that manufacturers must use to convey those messages.

a. Current Regulatory Regime (Labeling Expression)

FDA's current regulations contain a number of prescribed statements that manufacturers must include, word-for-word, in their labeling under certain circumstances. Some of these requirements apply to drugs used in specific populations, and others apply to drugs containing certain ingredients. For example, where "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)" with respect to a particular drug, FDA does not merely require that the drug's labeling report this result. Rather, FDA requires that the precise following statement appear in its entirety on the operative labeling of such a drug:

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[291] Even if FDA's formatting requirements were found not to withstand constitutional scrutiny, the agency could largely achieve the same goals by making the format requirements voluntary and providing manufacturers a safe harbor from enforcement actions if they comply with them.

> Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(*s*) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.[292]

Similarly, for drugs used in geriatric populations whose "clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences," FDA requires the operative labeling to include the following statement:

> Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.[293]

FDA's regulations also include a number of requirements that specific statements appear on drugs containing certain ingredients. To name only two examples, FDA requires the following statement on the operative labeling of drugs containing sulfites:

> Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.[294]

For drugs for human use with thyroid hormone activity, FDA requires the following statement to appear on the operative labeling as a boxed warning:

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[292] 21 C.F.R. § 201.57(f)(6)(i)(a).

[293] *Id* § 201.57(f)(10)(ii)(A).

[294] *Id.* § 201.22(b).

> Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.[295]

Other examples of FDA's ingredient-specific required warnings abound.[296]

In addition to these prescriptive regulations, FDA often uses more informal means effectively to dictate the precise language that manufacturers must use on their operative labeling – *e.g.*, by suggestions made during face-to-face meetings concerning drugs that are awaiting FDA approval.

b. Current Enforcement Mechanisms (Labeling Expression)

As with FDA's labeling requirements of both substance and format, FDA has a number of tools – including pre-approval and misbranding authority, enforced through injunction, seizure, criminal fines, and imprisonment – to compel manufacturers to comply with its regulations mandating that manufacturers convey messages using FDA's prescribed means of expression.[297] FDA's pre-approval authority is a particularly effective tool with which to insist upon nonsubstantive wording changes that are not specifically mandated in FDA's regulations. FDA can, either explicitly or implicitly (*e.g.*, regulation by raised eyebrow),[298] threaten to withhold approval for a product until the manufacturer complies with FDA's requested wording changes. The delay between approval of everything except specific language and approval to launch can be significant.

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[295] *Id.* § 201.316(b).

[296] *See id.* §§ 201.20 to .22, .300 to .323.

[297] *See supra* Part III.A.2, at 67.

[298] *See supra* Part III.B.2.b, at 81.

c. Is the Restriction a Restraint on Protected Speech? (Labeling Expression)

Protected Speech? A manufacturer's choice of the specific wording of a particular substantive message constitutes expressive activity that does not concern unlawful conduct and is not otherwise exempt from the guarantees of the First Amendment.[299] Thus, the First Amendment protects the speech at issue in FDA's wording regulations.

Severity of Restraint: FDA's requirement that a manufacturer use specific words to convey a particular substantive message on a drug's operative labeling before FDA will approve the drug operates as a prior restraint on speech, triggering a presumption against the constitutionality of such a regulation.[300]

Speech Restriction Incidental to Conduct Regulation? This type of operative labeling regulation impinges most significantly upon manufacturers' free speech rights, as it dictates the precise words that a manufacturer must use to convey a specific message. Although FDA's operative labeling regulations of substance and format can reasonably be viewed as part of FDA's overall regulation of manufacturers shipping drugs into interstate commerce, the same cannot be said for FDA's regulation of the specific words that appear on the operative labeling. FDA already controls the substance of the operative labeling to ensure that it contains all important use-related information and warnings and the format of the operative labeling to ensure that doctors can readily understand and digest this information. FDA's additional regulation of the precise wording of certain messages contained in the operative labeling, however, cannot presumptively be said to be part of FDA's overall regulation of manufacturer conduct to ensure safe and effective drug use. Rather, such regulations directly target a

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[299] *See supra* Part II.C, at 49-50.

[300] *See supra* Part II.B, at 41-42.

manufacturer's chosen form of expression and are not incidental to FDA's regulation of manufacturer conduct in shipping drugs into interstate commerce.

Relevant Legal Standard: FDA's wording regulations directly burden a manufacturer's free speech rights; the burdened speech is noncommercial and concerns lawful activity. Therefore, the regulations must be analyzed under the strict scrutiny standard.[301]

d. What Substantial, Legitimate Interest Does the Restraint Serve? (Labeling Expression)

FDA presumably would claim that its wording regulations, like its substantive and format regulations, serve a legitimate interest in ensuring that important drug use information is presented on the operative labeling in a truthful, nonmisleading manner and are not obscured by the manufacturer, thereby facilitating safe and effective drug use. As previously discussed, the legitimacy of FDA's interest in avoiding unsafe or ineffective drug use is beyond serious question.[302]

e. Does the Restraint Directly Advance a Legitimate Interest? (Labeling Expression)

FDA's wording restraints, as opposed to its substantive requirements, do not directly advance its interest in ensuring safe and effective drug use. Required drug use information will already be presented in an accurate, complete, readable and useful manner for physicians because of FDA's content and format requirements, and FDA's ability to require manufacturers to convey substantive messages is beyond dispute. FDA's prescriptive regulations of specified means of expression, however, is unnecessary. No substantial government interest is directly and materially advanced – and the public interest in obtaining timely access to valuable new

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[301] *See supra* Part II.B, at 48-49.

[302] *WLF*, 13 F. Supp. 2d at 69; *supra* Part III.B.1.d, at 78.

treatments can be materially thwarted – when FDA delays the introduction of these treatments merely to regulate the precise wording of already agreed-upon substantive information to be conveyed. "[T]he government, even with the purest of motives, may not substitute its judgment as to how best to speak for that of speakers and listeners ... ."[303]

f. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Labeling Expression)

FDA already has extensive substantive and formatting regulations that ensure that the operative labeling will accurately and completely convey required messages and that those messages will be readily understood. These regulations alone, coupled with FDA's pre-approval review process, constitute a more narrowly tailored alternative that adequately serves FDA's interest, which Pfizer fully supports. Such regulation would be consistent with the practice of other administrative agencies. The Federal Aviation Association ("FAA"), for example, requires that commercial airlines brief passengers on certain essential safety information before takeoff, such as "when, where, and under what conditions smoking is prohibited," "[t]he location of emergency exits," "[t]he use of safety belts," and "[t]he location and use of any required emergency flotation means."[304] The FAA does not, however, dictate the precise words that airlines must use to convey these messages.[305]

FDA also could convert its currently mandatory wording regulations into optional safe harbors. Pursuant to such an approach, manufacturers would have the option of conveying

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[303] *Riley v. Nat'l Fed'n of the Blind of N.C.*, 487 U.S. 781, 790-91 (1988) (rejecting State's "paternalistic premise the charities' speech must be regulated for their own benefit"); *see also Democratic Party of the United States v. Wisconsin ex rel La Follette*, 450 U.S. 107, 123-24 (1981) (observing that "a State, or a court, may not constitutionally substitute its own judgment for that of the Party" and that "as is true of all expressions of First Amendment freedoms, the courts may not interfere on the ground that they view a particular expression as unwise or irrational").

[304] 14 C.F.R. § 127.571.

[305] *Id.*

particular messages in the wording selected by FDA or in their own wording. If a manufacturer chose to use FDA's words, FDA would then guarantee that it would not exercise its enforcement authority against that particular statement by claiming that it is false or misleading. If a manufacturer chose to use its own words, FDA would retain the option of determining whether the communication was substantially adequate. The agency would, of course, need to demonstrate in an enforcement context that the manufacturer's wording choice is misleading and does not adequately present the required substantive information, preferably in an informal hearing process to be established by FDA as recommended in Part II.C.4.a. In such a case, FDA could then require the manufacturer to change its wording on the operative labeling. Such a regime imposes a lesser burden on speech than FDA's current prescriptive system.

g. Recommended Rule and/or Policy Change (Labeling Expression)

Based on the foregoing, Pfizer recommends that FDA convert all of its wording requirements into optional safe harbors, allowing manufacturers to choose how to convey particular messages but also guaranteeing not to challenge particular statements if manufacturers choose FDA's preferred means of expressing a particular message.[306]

FDA's liberalization of its prescriptive wording requirements would enhance the public hereto by permitting communications to be optimized and would not be entirely without

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[306] To provide a further incentive for manufacturers to comply with what FDA deems to be best practices, FDA also should commit to challenge, on conflict preemption grounds, any state-law-based claim of failure to warn which relates to safe harbor language. FDA has recently advanced such preemption claims, arguing in one case that "A State May Not Hold A Drug's Manufacturer Liable For Having Omitted A Warning That Would Have Misbranded The Drug In Violation Of Federal Law." Amicus Brief for the United States in Support of the Defendant-Appellee and Cross-Appellant, and in Favor of Reversal of the District Court's Order Denying Partial Summary Judgment to Defendant-Appellee and Cross-Appellant, *Motus v. Pfizer Inc,* at 15-16 (9th Cir. Sept. 3, 2002) (No. 02-55498); *see also* Statement of Interest of the United States of America, *In re Paxil Litigation*, at 4 (C.D. Cal. 2002) (CV-01-07937 MRP (CWx)) (objecting to court's entry of preliminary injunction based on allegedly false and misleading prescription drug advertising claim where FDA already had found claim to be truthful).

precedent. In the closely related OTC context, FDA already has recognized that a less restrictive approach than requiring prescriptive language would advance its goal of ensuring truthful, nonmisleading labeling. In a 1986 rulemaking, FDA relaxed its specific wording requirements for stating indications for use on OTC drug labeling and instead allowed manufacturers to select whether to use FDA's suggested language; their own truthful, nonmisleading language; or other truthful, nonmisleading alternatives:[307]

> After careful review and study, ... the agency now believes that the goal of ensuring truthful, nonmisleading labeling without inhibiting effective consumer communication does not require the enforcement of a rigid exclusivity policy. Recognizing that, within limits, there can be various ways of accurately stating the same thing, some of which may even be more meaningful to potential purchasers of OTC drug products, the agency has concluded that it can meet its responsibilities by providing greater flexibility for the use of alternative truthful statements without recourse to the time- and resource-consuming monograph amendment process. [308]

The agency further advised that it would use its prior required language as the benchmark for determining whether manufacturers' selected alternative language was false or misleading and observed that its new approach would be less costly and more efficient.[309] Just as FDA recognized that manufacturers could be given flexibility to express OTC indications in their own words without sacrificing – and perhaps enhancing – accuracy, so, too, should the agency extend this principle to prescription drug operative labeling. Allowing manufacturers to convey required substantive messages in the manner they deem most appropriate would not only enable

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[307] FDA, *Labeling of Drug Products for Over-the-Counter Human Use: Final Rule*, 51 Fed. Reg. 16,258, 16,266 (May 1, 1986).

[308] *Id.* at 16,259-60.

[309] *Id.* ("Rather, the agency will use the monograph language as its standard in determining whether alternative statements are accurate or require regulatory action, thus achieving its goals at a lower cost in terms of administrative and enforcement resources.").

FDA to focus its enforcement energies on labeling that does, in fact, risk misleading physicians but would also alleviate the constitutional tensions created by FDA's current approach.

C. FDA'S ABILITY TO REGULATE SPEECH CONCERNING DRUGS UNDERGOING THE APPROVAL PROCESS

As previously discussed, FDA can bar a manufacturer from promoting and selling a product for health-care uses where the agency has not approved that product to be marketed as a drug. Such commercial speech concerns unlawful conduct and is constitutionally unprotected under the first prong of *Central Hudson* analysis.[310] Just as clearly, FDA cannot bar a person who is not selling a product from making health claims about the product. Such speech is noncommercial scientific speech and therefore subject to full First Amendment protection under *Keyishian*.[311] The analysis below deals with FDA's power to regulate speech that might be deemed to be somewhere in the middle – manufacturer speech concerning a product already in the approval process but not yet approved or marketed for any drug use. [312]

Under FDA's current approach, the agency bans all but scientific and SEC-required speech about drugs undergoing the approval process. Unlike speech about chemical entities that a manufacturer does not seek to market as a drug, at least some pre-approval speech might arguably be considered to be commercial – and subject to the *Central Hudson* analysis instead of

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[310] *See supra* Part II.C.4, at 49-50 (discussing *Cent. Hudson*, 447 U.S. at 566); *see also Pittsburgh Press*, 413 U.S. at 389.

[311] *See supra* Part. II.C.1, at 48-49 (discussing *Keyishian*, 385 U.S. at 603).

[312] This section does not analyze manufacturer speech about products for which a manufacturer has not yet sought status as an Investigational New Drug ("IND"). If the product is already on the market for a non-drug use, speech relating to its potential use as a drug would be subject to the jurisdictional analysis set forth in *supra* Part III.A, at 65-71. If the product has not yet been marketed for any use, the speech would constitute noncommercial, scientific speech and warrant full First Amendment protection, as it may be years, if ever, until the product successfully completes FDA's approval process and reaches the market. This section also does not consider speech about products that are approved for one or more uses but being reviewed for additional uses. That issue is dealt with in the "off-label" use section in Part III.E below.

strict scrutiny – because it concerns products that the manufacturer seeks to sell in the future. Although FDA can prohibit demonstrably false and misleading speech concerning products in FDA's approval pipeline,[313] the agency cannot simply ban all such speech categorically, regardless of its actual truth. Moreover, while the agency has an indisputably substantial interest in protecting the public from unsafe drugs, the speech restrictions do not directly advance this interest because there is no risk of any immediate harm to patients when the products addressed are not yet being sold.

Thus, FDA's near-categorical ban on such speech is too broad in light of the First Amendment's countervailing interest in ensuring the uninhibited dissemination of scientific information and truthful commercial information. Instead, the agency should consider the more narrowly tailored regulatory alternatives suggested below, including mandatory disclosures and the targeted use of corrective advertising where appropriate. FDA's current suppressive approach, if left unchanged, would be unable to withstand a First Amendment challenge.

1. Current Regulatory Regime (Pre-Approval Speech)

FDA's current regulations prohibit all pre-approval advertising except for "institutional" and "reminder" ads, neither of which permits the manufacturer to make any claims regarding the safety or effectiveness of the drug.[314] Rather, "institutional advertisements" merely link the drug manufacturer to a field of research concerning a particular disease or condition but are not permitted to specify a product name.[315] "Coming soon" announcements advertise only the name of a new product and are not permitted to suggest potential indications, make claims of safety or

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[313] *See supra* Part II.C.4.a, at 54.

[314] FDA, Division of Drug Advertising and Labeling, Reissuance of Pre-Approval Promotion Guidance, August 1986 (FDA Industry-wide letter). Off-label speech is addressed in other guidance documents.

[315] *Id.*

effectiveness, or contain any graphic representations.[316] Moreover, the agency allows manufacturers to use only one form of pre-approval advertisement for a product and bars them from switching between the two. If a drug is known or likely to bear a boxed warning in its labeling, FDA mandates that only the institutional format of advertising be used.[317]

The agency does appear to allow very limited leeway for manufacturers to engage in scientific, noncommercial speech concerning unapproved products not yet on the market and accepts press releases which provide SEC-mandated disclosure to investors. For example, the agency states in a guidance document that it "shall not object to company sponsored symposia which offer an opportunity for scientific dialogue in the milieu of research. Drug companies may not, however, create reports or proceedings reprints of such symposia to be distributed by sales representatives *before* the new product is approved ... ."[318] FDA further cautions that manufacturers should not "display[] or disseminat[e] at commercial exhibits at medical meetings so-called 'educational materials' or other promotional materials regarding or suggesting use of unapproved products, indications, dosage forms and/or schedules. Invitations or other referrals to 'scientific' exhibits or proceedings which provide the same type of information are considered as causing that information to be regarded as 'commercial' when issued from commercial sources." FDA also warns manufacturers that they should "[c]onfine educational efforts for unapproved products, indications, dosage forms and/or schedules to the scientific exhibit area.

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316 *Id.*

317 *Id.*

318 *Id.*

Educational efforts in commercial exhibit areas should be confined to information normally provided in the product's approved labeling."[319]

2. Current Enforcement Mechanisms (Pre-Approval Speech)

FDA's means of enforcing this sweeping ban on pre-approval promotional speech are limited. As a practical matter, the agency cannot rely on its seizure power because there is no product on the market to seize. Nor can FDA invoke its other misbranding remedies of injunction and criminal prosecution in the absence of a marketed product to deem misbranded. Nonetheless, FDA still wields considerable *in terrorem* power over manufacturers. FDA may exercise this power overtly, *i.e.*, by threatening to suspend the product approval process until the manufacturer stops engaging in pre-approval speech and perhaps even issues corrective advertising – or more covertly, *i.e.*, by "regulating by raised eyebrow," as discussed above.[320]

3. Is the Restriction a Restraint on Protected Speech? (Pre-Approval Speech)

As explained below, FDA's restrictions in this area operate by directly banning speech – at least during a certain period of time – for reasons that cannot be justified as serving a non-speech function. Accordingly, these restraints are subject to heightened scrutiny under the First Amendment.

Protected Speech? The pre-approval speech that is the subject of FDA's suppressive restrictions does not propose unlawful activity because there is no underlying unlawful sale to which the speech attaches, nor could it be deemed false or inherently misleading as a general rule. Thus, FDA cannot argue that *Pittsburgh Press* exempts pre-approval speech from

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[319] *Id.*

[320] *See supra* Part III.B.2.b, at 67, 81.

traditional First Amendment guarantees altogether.[321] Only one possible scenario might bring pre-approval speech within *Pittsburgh Press*: the agency might be able to show that the manufacturer is disseminating the information to encourage illegal purchases of the drug – *e.g.*, via online sales involving unlawful importation of the drug from other countries. Yet even here, if the drug maker itself is not responsible for unlawfully importing the product, courts would likely require the government to act against the unlawful act of importation itself rather than chill the manufacturer's truthful speech about a product it is seeking to bring lawfully to market.

As is the case with all truthful information, there is a societal benefit from allowing its uninhibited dissemination. For example, consider a proposed ad concerning a new drug that may help patients avoid or defer an elective surgical procedure. The ad proposes to describe the drug and suggests that patients consult their physicians about deferring surgery until the drug is available. FDA's current regulations would clearly prohibit such an ad because it makes an efficacy claim about a not-yet marketed product and goes beyond the permissible boundaries for coming soon and institutional ads.

Assuming that this information is truthful, however, it is clearly in the public interest for the manufacturer to be able to disseminate it. The ad will enable clients and doctors to make treatment evaluations for this indication armed with more information about soon-to-be available products.[322] First Amendment case law strongly supports the purchaser's interest in upcoming product information as going to the core rationale for protecting commercial speech – *i.e.*, to

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[321] *See supra* Part II.C.2, at 49-50 (discussing *Pittsburgh Press*, 413 U.S. at 388-89).

[322] *See supra* Part I.B-C, at 3-17 (discussing benefits of consumer empowerment, new paradigm for doctor-patient relationship, and role of increased flow of information in serving that paradigm).

assist a would-be purchaser in making choices between products by providing him or her with complete and accurate information about those products.[323]

In light of the undisputed value of pre-approval speech concerning products that will soon be lawfully marketed, that speech is subject to the First Amendment's usual protections, which may vary to some extent depending on whether the speech at issue is deemed to be commercial or noncommercial.[324]

Severity of Restraint: The regulations in this category ban almost all pre-approval advertising for a prolonged period of time and therefore impose the most severe type of speech suppression of all. Because they coincide in time with the drug approval process, these restrictions allow FDA considerable scope to dictate – or strongly suggest – the content of what little advertising is permitted during the period. Under the general First Amendment presumption against such speech suppression, these restraints should be scrutinized particularly closely because they are expressly designed to curtail the flow of information.[325]

Speech Restriction Incidental to Conduct Regulation? FDA's restrictions in this area directly target speech *qua* speech. By definition, the regulations do not directly affect the marketing of any product, for there is no product yet being sold. Accordingly, these restraints do not qualify for the more forgiving *O'Brien* standard of First Amendment review.[326]

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[323] *See Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 765 (1976) ("It is a matter of public interest that [private economic] decisions, in the aggregate, be intelligent and well informed. To this end, the free flow of commercial information is indispensable."); *Thompson v. W. States Med. Ctr.*, 122 S. Ct. 1497, 1503 (2002) (quoting *Va. State Bd. of Pharmacy*); *supra* Part II.B, at 39-47.

[324] *See supra* Part II.C.1 and 4, at 48-49, 52-63.

[325] *See Org. for a Better Austin*, 402 U.S. at 418-19; *supra* Part II.B, at 41-42.

[326] *See supra* Part II.C.3, at 51-52 (discussing *O'Brien*, 391 U.S. at 376).

Relevant Legal Standard: The speech at issue in this area is subject to either strict scrutiny[327] or heightened scrutiny under *Central Hudson*.[328] The distinction in a particular case turns on whether the speech is appropriately categorized as noncommercial scientific speech or commercial speech. Either way, however, the First Amendment imposes significant obstacles on FDA's power over pre-approval speech.

Much, if not all, manufacturer speech about as-yet unmarketed products is arguably not commercial speech at all, for it is logically impossible to "propose a commercial transaction" when the product is not yet available for purchase. The agency therefore must be sensitive to the need to determine whether certain pre-approval communications are, in fact, properly categorized as noncommercial – at least from FDA's regulatory standpoint[329] – and therefore fully protected under the First Amendment.

For example, manufacturers often engage in noncommercial, scientific speech concerning products in development. Such speech could well occur within the context of scientific discussion, with a back-and-forth exchange of information involving speakers not subject to FDA regulation. Specifically, research scientists or physicians employed by a drug company might wish to participate in a symposium to exchange views with academic researchers and eminent specialists concerning the potential health benefits of particular chemical entities based

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[327] *See supra* Part II.C.1, at 48-49.

[328] *See supra* Part II.C.4, at 52-63 (discussing *Cent. Hudson*, 447 U.S. at 566).

[329] *See infra* Part III.D, at n. 420 (discussing manufacturer communications to the investment community, which are regulated by the SEC, not FDA, as noncommercial speech because it involves sales of interest in the firm itself – not in the firm's products).

on preliminary studies. Such a robust marketplace of ideas is precisely what the First Amendment aims to foster.[330]

Moreover, it is possible that other, unregulated speakers engaged in this exchange may deliver substantially the same, if not identical, messages to that of the regulated entity. As the Supreme Court has repeatedly held, "[e]ven under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtual identical messages are in serious tension with principles undergirding the First Amendment."[331] FDA may not simply presume, as it now does, that otherwise scientific information will "be regarded as 'commercial' when issued from commercial sources."[332] Engaging in knee-jerk discrimination against a speaker based solely on the speaker's identity cannot withstand constitutional review.[333] As a practical matter, this means that the agency must, at a minimum, develop justifiable standards for distinguishing when a manufacturer's pre-approval communications must be treated as fully protected noncommercial speech.

Certain types of pre-approval speech could be deemed commercial because they explicitly encourage future purchases of the product for a particular use – *e.g.*, the DTC ad

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[330] *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 70 (D.D.C. 1998) ("*WLF*") (stating "the Supreme Court has repeatedly rejected governmental attempts to equate less information with better decision-making"), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000); *44 Liquormart*, 517 U.S. at 503-04 (quoting *Edenfield v. Fane*, 507 U.S. 761, 767 (1993) ("'But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.'")).

[331] *Greater New Orleans Broad. Ass'n v. United States*, 527 U.S. 173, 193-94 (1999); *accord First Nat'l Bank of Boston v. Bellotti*, 435 U.S. 765, 784-85 (1978) (holding that government "is constitutionally disqualified from dictating . . . the speakers who may address a public issue"); *see also supra* Part II.B, at 41.

[332] FDA, Division of Drug Advertising and Labeling, Reissuance of Pre-Approval Promotion Guidance (Aug. 1986) (FDA industry-wide letter).

[333] *See supra* Part II.B, at 41 (discussing judicial rejection of speaker-based discrimination).

promoting a soon-to-be-launched product discussed above. Even so, such communications would enjoy substantial protection under *Central Hudson*.[334]

4. What Substantial, Legitimate Interest Does the Restraint Serve? (Pre-Approval Speech)

As a threshold matter, the pre-approval speech restraints cannot serve any interest in protecting the drug preclearance system because the pre-approval speech at issue concerns drugs that already are undergoing FDA's approval process. Moreover, FDA's substantial interest in preventing consumer harm as a result of inappropriate reliance on misleading promotional statements is attenuated in this context because the products that the statements concern are not yet available for purchase.

FDA could, however, presumably point to its interest in maintaining a pure and honest marketplace for drugs, where doctors and consumers may depend upon the reliability of manufacturers' representations concerning the products they vend. Certainly, that interest coincides with FDA's original, limited mission under the 1906 Act to serve as the guarantor of accurate claims made about drugs on their label.[335] This core interest in policing drug label claims antedates even FDA's mandate to ensure basic drug safety, which did not arise until many years later under the 1938 FDCA.[336] Thus, if FDA is able to demonstrate the falsity or misleading nature of a claim before a product is approved, FDA's interest in preserving the integrity of the marketplace and in preventing further confusion concerning the uses of the product would give constitutional sanction to prohibiting the manufacturer from continuing to

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[334] *See supra* Part II.C.4, at 52-63 (discussing *Cent. Hudson*, 447 U.S. at 566).

[335] *See supra* Part II.A.3.a, at 27-29.

[336] *See supra* Part II.A.3.b, at 29-31.

make that claim, assuming that FDA had the necessary statutory authority absent a marketable product.

To the extent, however, that FDA invokes this interest to support regulations that categorically ban virtually all pre-approval statements as presumptively false or misleading until the agency has had the chance to verify their truth, the agency would be misusing the interest. Well-settled First Amendment principles flatly condemn such draconian restrictions on the communication of commercial information in the absence of a demonstrable basis for calling into question the truthfulness of the statements at issue.[337] While the agency appropriately may regulate statements to ensure their veracity if their truthfulness is demonstrably suspect, it cannot act as a unilateral speech filter through which only messages that the agency believes to be suitable for communication to the public may pass.[338]

FDA would strengthen its interest in regulating if it could show that certain statements about a product undergoing FDA approval are not only false or misleading but also linger in doctors' and consumers' minds after the product is approved and marketed, causing doctors to prescribe drugs in inappropriate ways, which then harms consumers.[339] Again, however, FDA cannot simply assert, without proof, that speech concerning a particular drug is false or misleading or that the speech may induce doctors to misprescribe, or consumers to misuse, a

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[337] *See, e.g., Zauderer v. Office of Disciplinary Counsel,* 471 U.S. 626, 646 (1985) ("[T]he free flow of commercial information is valuable enough to justify imposing on would-be regulators the costs of distinguishing the truthful from the false, the helpful from the misleading, and the harmless from the harmful."); *accord Ibanez v. Fla. Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 143 (1994); *see also supra* Part II.C.4.a, at 54.

[338] *See Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (rejecting restraint on dietary supplement claims unless FDA could demonstrate that "evidence in support of a claim is outweighed by evidence against the claim"); *WLF*, 13 F. Supp. 2d at 67 ("In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.").

[339] *See WLF*, 13 F. Supp. 2d at 69 (acknowledging importance of FDA's interest in ensuring safe and effective drug use).

particular drug once it does enter the market in misplaced reliance on the unsupported claim. Rather, *Central Hudson* requires FDA to substantiate its assertions in order to justify a blanket ban on such speech.[340]

5. Does the Restraint Directly Advance a Legitimate Interest? (Pre-Approval Speech)

FDA's near total ban on pre-approval speech does not directly and materially advance FDA's interest in preventing the potential harms that might arise from misuse based on pre-approval messages that might not be substantiated at the end of the drug approval process, as the third prong of *Central Hudson* requires.[341] Even if pre-approval speech were freely allowed, the risk that such harm would occur is highly unlikely given that (1) the drugs are not yet available for purchase; (2) even when they become available, a consumer could obtain them only through a doctor's prescription; and (3) that doctor then will have ready access to FDA-approved operational instructions for the safe and effective use of the product. The draconian restriction of banning virtually all pre-approval speech outright is almost superfluous to the advancement of FDA's public health interest – and therefore does not directly and materially advance that interest – in light of the many other built-in safeguards of the prescription drug approval process.

6. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Pre-Approval Speech)

There are several more targeted means of serving FDA's arguably substantial interest identified above. The current ban on pre-approval speech suppresses information about claims that ultimately *will* be approved by FDA in addition to claims that may not. First Amendment

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[340] *See supra* Part II.C.4.a, at 54 (establishing that regulator must show that speech at issue is false or misleading); *supra* Part II.C.4.b, at 59-60 (demonstrating that regulator must establish that "the harms it recites are real" (citing *Edenfield*, 507 U.S. at 770-71)).

[341] *See Edenfield*, 507 U.S. at 770-73; *supra* Part II.C.4.c, at 60.

precedent plainly favors the more targeted alternatives over the effective suppression of truthful and useful information about drugs being reviewed for the marketplace.[342]

First, FDA plainly could ban pre-approval claims that it is able to establish affirmatively are false or misleading.[343] Such an approach would target only the demonstrably offending claims and would serve as an effective prophylactic measure to guard against consumer drug misuse based on such claims.

Second, if the agency is able to establish that a manufacturer has made false, misleading, or otherwise unsupported pre-approval claims, the agency could simply to refuse to approve the drug for marketing until after an appropriate period of time has passed to allow any misleading effect from the unsupported claims to dissipate. Such an approach, however, would have the harmful effect of delaying market entry of valuable new treatment options that FDA has determined to be safe and effective for their intended uses.

If FDA is unable to demonstrate that a particular claim is false or misleading but can establish that the claim has the potential to mislead, the agency could require manufacturers making pre-approval safety and efficacy claims to disclose (1) that those claims are based on preliminary studies, with the source of the studies and whether they have been peer-reviewed prominently indicated, (2) that they have not yet been evaluated or approved by FDA, and (3) that they might not be borne out by studies now underway.[344] Requiring such disclosures would ensure that the speech does not mislead readers into believing that FDA has endorsed the

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[342] *See supra* Part II.C.4.d, at 61-62.

[343] *See Cent. Hudson*, 447 U.S. at 593 ("[F]alse and misleading commercial speech is not entitled to any First Amendment protection."); *supra* Part II.C.4.a, at 54.

[344] *See supra* Part II.B, at 44-46 (discussing *Pearson*).

claim.[345] Moreover, where a pre-approval safety or efficacy claim does ultimately prove to be unsubstantiated, but the product nonetheless reaches the market on the basis of other claims, FDA could require the manufacturer to take reasonably necessary action, including corrective advertising, to correct any lingering mistaken impressions based on the unsupported claim.[346]

This regulatory alternative is in accord with the First Amendment's strong preference for requiring additional information disclosures instead of suppressing speech outright as the first regulatory line of defense to guard against any harmful effects from potentially misleading speech.[347] Moreover, as shown below, this less restrictive approach will advance FDA's interest in ensuring that marketed products are used safely and effectively regardless of FDA's ultimate determination whether those claims are substantiated:

- Where the product is ultimately not approved for any uses and never marketed, no cognizable harm will ever result from unsubstantiated safety and efficacy claims about the product, as consumers will not be able to purchase the product. If the product is unlawfully marketed despite its lack of FDA approval, the appropriate non-speech remedies are seizure, injunction, and, if applicable, criminal penalties.
- Where the product is ultimately approved for all of the uses which the safety and efficacy claims address, no harm will arise from the dissemination of the preliminary claims because they were ultimately found to have been substantiated.

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[345] *See supra* Part II.B, at 44-46.

[346] *See Warner-Lambert Co. v. FTC*, 562 F.2d 749, 756 (D.C. Cir. 1977) (upholding FTC's power to issue corrective advertising where "a hundred years of false ... claims have built up a large reservoir of erroneous consumer belief which would persist, unless corrected, long after petitioner ceased making the claims" but warning that First Amendment requires advertising requirement to be "no greater than necessary to serve the interest involved"); *id.* at 762 (observing that corrective advertising is appropriate where (1) misleading ads "play a substantial role in creating or reinforcing in the public's mind a false belief about the product" and (2) "this belief linger[s] on after the false advertising ceases"); *Novartis Corp. v. FTC*, 223 F.3d 783, 789 (D.C. Cir. 2000) (upholding corrective advertising against First Amendment challenge).

[347] *See Bates v. State Bar of Ariz.*, 433 U.S. 350, 376 (1977) ("[T]he preferred remedy is more disclosure, rather than less ...."); *Pearson,* 164 F.3d at 657 ("In more recent cases, the [Supreme] Court has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression."); *supra* Part II.B, at 44-46.

- Where the product is approved for some, but not all, uses, a manufacturer may have made pre-approval claims about a use that FDA later decides not to approve. In this case, there is some risk that doctors and/or consumers will remember the prior unsubstantiated claims and mistakenly believe that the product has been approved for those uses. If FDA can demonstrate that such confusion exists on an ongoing basis, FDA could require the manufacturer to take the corrective action described above.

In sum, this type of nuanced, case-by-case approach is far more in accord with First Amendment jurisprudence than the outright ban up front, which FDA's regulations now impose.

7. Recommended Rule and/or Policy Change (Pre-Approval Speech)

FDA could best square its current approach to pre-approval speech with the First Amendment by discarding its effective ban on most pre-approved speech and replacing it with:

(a) a ban only of demonstrably false speech;

(b) requirements of tailored disclosures concerning potentially misleading pre-approval speech – including disclosures that the claims made are based on preliminary studies, have not yet been approved by FDA, and may ultimately never be approved; and

(c) a requirement that a manufacturer take corrective action where FDA can demonstrate that a potentially harmful spillover effect exists from unsubstantiated claims made during the pre-approval phase.

This combination of more precisely crafted regulations will discourage unscrupulous manufacturers from overreaching in making unsubstantiated claims about as-yet unlaunched products while also allowing responsible manufacturers appropriate latitude to engage in truthful, non-misleading speech about drugs still in FDA's review pipeline.

D. FDA'S ABILITY TO REGULATE ADVERTISING AND OTHER PROMOTIONAL SPEECH CONCERNING APPROVED DRUG USES

In this section, Pfizer focuses on FDA's authority to regulate advertising and other "promotional communications"[348] concerning approved uses of prescription drugs.[349] Unlike a

[348] For the purpose of these comments, the term "promotional communications" includes all information vehicles that are not within the considerably narrower term "operative instructions for use" or "operative labeling," which Pfizer has limited to the label and professional labeling, or package insert. *See supra* Part III.B, at 71-74. Thus,

product's operative labeling, the purpose of advertising and other promotional communications is not to instruct doctors or consumers on how to use a drug safely and effectively for an approved indication but rather to pique interest in or otherwise draw attention to the product to encourage physicians to consider prescribing it and/or consumers to ask their doctor about it. Pfizer's analysis of prescription drug advertising of approved uses is driven by its belief that this material should not – and constitutionally cannot – be regulated in the same manner as operative labeling, which forms an inherent part of the drug itself,[350] but instead is subject to the same heightened protection under the First Amendment afforded to other types of commercial speech.

Pfizer first briefly summarizes FDA's historical regulation of prescription drug advertising, including the agency's understandable, but arguably misguided, reluctance to allow manufacturers to promote prescription drugs in the same manner as other products. Pfizer also explains why the agency's current approach, although uncontroversial in 1962 when FDA was first given jurisdiction over prescription drug advertising, is now constitutionally suspect in the wake of the Supreme Court's more recent pronouncements concerning the value of commercial speech and its protection under the First Amendment. Pfizer then analyzes the constitutionality of FDA's current advertising regulations in detail – discussing separately promotional communications directed to professionals and those targeted to consumers – and suggests

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certain communications that FDA treats as "labeling," such as brochures, mailing pieces, and detailing pieces are treated here as "promotional communications." Unless otherwise indicated, use of the terms "advertising" or "advertisement" in these comments refers both to traditionally formatted ads and also to promotional communications that fall under 21 C.F.R. § 202.1(l)(2)'s broad definition of "labeling"; the legal analysis does not vary simply because the format of the messages may differ.

[349] The constitutional considerations surrounding FDA regulation of speech about off-label uses are set forth in Section III.E, *infra* at pp. 155-65.

[350] *See supra* notes 252-58 and accompanying text.

modifications that FDA can make to bring its advertising regime in line with governing First Amendment principles.

As explained in more detail below, while Pfizer supports stringent FDA supervision of a prescription drug's operative labeling,[351] it believes that FDA's current advertising regime is overly restrictive, inconsistent with constitutional mandates, and may actually detract from FDA's responsibilities as the gatekeeper over the introduction of safe and effective drugs into the marketplace. Pfizer urges FDA to focus its regulatory energies on ensuring complete, accurate, and easily understandable operative labeling, to regulate prescription drug advertising only to the extent necessary to prevent false and misleading communications, and to require manufacturers clearly to distinguish between the two types of communications. Adopting this bifurcated approach to speech regulations will insulate FDA from further successful First Amendment challenges to its regulations like the one in *Western States*. It will also better enable FDA to accomplish its critical mission of protecting the public from unsafe and ineffective drugs by preventing inappropriate reliance on materials intended for promotional purposes only and by fostering appropriate reliance on operative labeling intended to provide comprehensive information on safe and effective drug use.

In engaging in this analysis, Pfizer does not attempt to define the best advertising practices but rather focuses on how the First Amendment limits FDA controls. FDA should not assume that manufacturers necessarily will adhere only to minimum regulatory standards in their advertising. Manufacturers' long-standing commitments to act responsibly and to maintain valued reputations and credibility, among other motivations, provide additional safeguards above

[351] *See supra* Part III.B.1, at 74-79.

and beyond FDA's regulations that will continue to ensure that manufacturer communications about their products will be informative. truthful and not misleading.

1. FDA's Regulation of Advertising

FDA's approach to prescription drug advertising is, in part, an artifact of the era when the agency did not have jurisdiction to regulate such advertising at all. Before the 1962 Amendments to the FDCA, FDA's authority to regulate manufacturers' communications about their products was confined to regulation of "labeling," while jurisdiction over advertising was vested in the FTC.[352] During this time period, FDA nonetheless exercised effective control over many promotional communications by categorizing them as "labeling" subject to its jurisdiction,[353] an approach that was understandable in light of the significant safety concerns that led Congress to expand FDA's mandate in both 1938 and 1962.[354] FDA's regulation of promotional materials as operative labeling rather than as advertising may explain why many of FDA's current advertising regulations seek to convert the promotional messages typically found in advertising into more neutral communications that provide the listener with comprehensive product information rather than interesting him or her in the product.

Congress acceded to the view that prescription drug advertising should be fully informative, rather than promotional, when it transferred jurisdiction over prescription drug advertising from the FTC to FDA and directed such advertising to disclose information

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[352] Wheeler-Lea Act, ch. 49, § 4, 52 Stat. 111, 114-15 (1938).

[353] *See Kordel*, 355 U.S. at 345 (upholding FDA's expansive interpretation of labeling). FDA's expansive interpretation of what constitutes labeling is highlighted by 21 C.F.R. § 202.1(l)(2), which lists eighteen specific types of labeling, including calendars and motion picture films.

[354] *See supra* Part II.A, at 19-39.

concerning not only a drug's effectiveness but its side effects and contraindications as well.[355] Taking that cue, FDA has, over time, issued pervasive,[356] extensive regulations that tightly control what manufacturers may say about their products and attempt to transmogrify advertising and other promotional communications into comprehensive instructional messages. As only one example of this practice, FDA continues to define "labeling" broadly to encompass a wide variety of promotional communications and bars those communications from being "promotional in tone."[357] Collectively, FDA's regulatory restraints and disclosure requirements reflect wariness about allowing drug manufacturers to engage in the same sort of promotional communications that other commercial speakers employ.[358]

FDA's wariness is particularly noteworthy in its regulation of DTC advertising. The agency effectively repressed these types of communications until 1982 by virtue of its silence on the subject; the pharmaceutical community took that silence, in conjunction with FDA's well-known, generally negative view of advertising, to signify that the agency was opposed to DTC ads.[359] In 1982, the then-Commissioner of FDA publicly predicted the exponential growth of DTC advertising; manufacturers read this speech as a signal that FDA no longer remained

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[355] Drug Amendments of 1962, Pub. L. No. 87-781, § 131(a), 76 Stat. 780, 791-92 (1962) (codified as amended at 21 U.S.C. § 352(n)); Memorandum of Understanding Between Federal Trade Commission and the Food and Drug Administration, 36 Fed. Reg. 18,539 (Sept. 16, 1971).

[356] David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising,* 264 JAMA 2409, 2410 (1990) (observing FDA's expansive view that its regulations reach "virtually all information disseminating activities by or on behalf of a prescription drug manufacturer").

[357] *See* 21 C.F.R. §§ 201.56(b), 202.1(l)(2).

[358] *See* 21 C.F.R. § 202.1; FDA, Notice, Request for Comments, Direct-to-Consumer Promotion, 61 Fed. Reg. 24314, 24316 (May 14, 1996) ("[T]he purpose of the brief summary requirement [is to] ensure that advertising conveys a balanced impression about the product's risks and benefits."); FDA, Notice of public hearing, request for comments, Pharmaceutical Marketing and Information Exchange in Managed Care Environments, 60 Fed. Reg. 41891, 41892 ("Underlying this [regulation of labeling and advertising] is a public health concern that health care professionals and patients base their decisions about drug products on sound scientific data and information.").

[359] *See* Wayne L. Pines, *FDA Advertising and Promotional Manual,* ¶ 441 (Thompson Publishing Group 2001).

opposed to DTC advertising.[360] As soon as manufacturers began preparing to act on this signal, however, FDA in 1983 requested a voluntary moratorium on such advertising until the agency could evaluate its potential effects,[361] citing the need for a period of "cautious restraint" in addressing this issue.[362] Despite some internal opposition to DTC advertising,[363] FDA lifted the moratorium two years later, at which time the agency made clear that all the regulations applicable to advertising in general would apply to DTC advertising.[364] Although FDA allowed DTC advertising both in print and on television after 1985, television advertising of prescription drugs to consumers was effectively squelched by disclosure requirements until 1997.[365] Even then, FDA made it clear that DTC television advertising was to be considered an experiment,[366] which the agency continues to study today.[367]

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[360] *See* Arthur Hull Hayes, Jr., Comm'r of Food and Drugs, Summarizing the State of Pharmaceutical Advertising, Address Before the Pharmaceutical Advertising Council (1982), *referenced in* Wayne L. Pines, *A History and Perspective on DTC Promotion*, 54 Food & Drug L.J. 489, 492 (1999).

[361] *See* Arthur Hull Hayes, Jr., Comm'r of Food and Drugs, Direct-to- Consumer Advertising of Prescription Drugs: Moratorium, Address Before Pharmaceutical Advertising Council (Feb. 17, 1983).

[362] *See* 50 Fed. Reg. 36677 (Sept. 9, 1985).

[363] *See* David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising,* 264 JAMA 2409, 2412 (1990).

[364] *Id.*

[365] The extensive DTC disclosure requirements essentially limited viable DTC messages on television to reminder and help-seeking ads. *See* FDA, Direct-to-Consumer Promotion, Public Hearing, 60 Fed. Reg. 42581, 42583 (Aug. 16, 1995).

[366] *See* FDA, Draft Guidance For Industry: Consumer-Directed Broadcast Advertisements (Aug. 1997). During the first year that DTC television advertising was allowed, the agency subjected nearly half of all DTC broadcast ads to enforcement actions. *See* Wayne L. Pines, *A History and Perspective on DTC Promotion*, 54 Food & Drug L.J. 489, 497 (1999).

[367] FDA, Guidance for Industry: Consumer-Directed Broadcast Advertisement, Aug. 1999, *available at* www.fda.gov/cder/guidance/index.htm (representing the Agency's *current* thinking on procedures to fulfill the requirements for disclosure of product information in connection with consumer-directed broadcast advertisements for prescription human and animal drugs, and human biological products (emphasis added)).

FDA's skepticism toward prescription drug advertising has led to a regime where manufacturers are precluded from using advertising for its intended purpose – *i.e.,* to attract attention to a product and highlight its benefits. Congress itself has long recognized and endorsed this essential role of advertising, even for drugs, as evidenced by its statement in a Senate Report leading up to the passage of the FDCA that "the law has long recognized the privilege of the advertiser to put his best foot forward in the sale of his wares."[368] Indeed, sellers of other products routinely rely on advertising to emphasize the advantages of their products. One has only to watch a laundry detergent ad to realize that the vendor does not have to disclose the stains that the detergent *cannot* remove in addition to the ones that it can, and no one would seriously argue that such an ad is misleading merely because it did not do so: the whole purpose of commercial speech is to highlight the benefits of the promoted product. FDA, by requiring manufacturers to include an exhaustive list of a product's risks as well as its benefits, not only dilutes the force and increases the cost of truthful, promotional messages that manufacturers wish to carry but also hampers drug manufacturers' ability to respond truthfully to attacks on their products.

Yet another anomaly in FDA's advertising regime is the government's use of its power to mandate presentation of at least one government-favored message that is not rooted in public health concerns – a drug's generic name. According to Congress, this required disclosure is designed not primarily to ensure safe and effective use of the product but simply to further the government's interest in promoting generic competition.[369] Forcing advertisers to convey

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[368] S. Rep. No. 73-493, at 124 (1934).

[369] *See infra* Part III.D.2.d, at 132-33.

government-sponsored messages that they might otherwise choose not to carry – especially messages supporting competitors – is inconsistent with the fundamental purpose of advertising.

It is certainly understandable why FDA for years has thought it could shy away from allowing more classic commercial speech for drugs and instead gravitated toward the tightly controlled and highly speech-restrictive system now in place. The agency's mission in protecting the public health from unsafe or ineffective drugs is undisputably important, evidenced by the tragic injuries and deaths resulting from unsafe drugs that preceded the enactment of both the 1938 and 1962 Acts.[370] Moreover, the fundamental underpinnings of prescription drug advertising were established at a time when courts gave commercial speech no First Amendment protection at all.[371] Thus, FDA was able to focus exclusively on its public health mission and the regulations that it believed would most effectively advance that mission, unfettered by constitutional constraints limiting what it could require manufacturers to say – or not to say – about their products in advertisements.

In light of the line of cases beginning with *Virginia State Board of Pharmacy* and continuing through *Western States*,[372] however, it has become increasingly apparent that a number of elements of FDA's highly speech-restrictive regime would not be able to withstand constitutional scrutiny if challenged today. More than a quarter-century of legal precedent makes clear that commercial speech serves the valuable function of informing purchasers about a particular product and that the First Amendment properly protects such speech.[373] Merely

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[370] *See supra* Part II.A.3.b, c, at 29-35.

[371] *See supra* Part II.C.4, at 52 (discussing *Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942)).

[372] *See Virginia State Board of Pharmacy v Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 757 (1976); *Thompson v. Western States Medical Center Western States,* 122 S. Ct. 1497 (2002).

[373] *See Bates*, 433 U.S. at 364 ("[S]ignificant societal interests are served by such speech. Advertising, though entirely commercial, may often carry information of import to significant issues of the day. And commercial speech

because such speech does not convey exhaustive information concerning the product does not render it false or misleading,[374] and the First Amendment protects sellers to engage in truthful commercial speech.[375] This includes the right to deliver messages of their choosing, rather than those of the government.[376] The First Amendment also allows sellers engaging in noncommercial speech, including speech that responds to attacks made by third parties on their products. It simply serves no public health purpose to inhibit a manufacturer, who is likely to be the most knowledgeable source of scientific data concerning a particular drug, from providing useful information about the drug when that drug's utility is thrown into public controversy by a third party.

In short, many of FDA's current advertising regulations are outmoded and constitutionally problematic. As described below, FDA should carefully evaluate its regulations to ensure not only that they acknowledge pharmaceutical manufacturers freedom to speak truthfully about their products but also that they do not convert prescription drug advertising into a platform for conveying mandated government messages not necessary to avoid false or misleading statements.

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serves to inform the public of the availability, nature, and prices of products and services, and thus performs an indispensable role in the allocation of resources in a free enterprise system."); *Virginia State Board of Pharmacy*, 425 U.S. at 757.

[374] *Bates*, 433 U.S. at 375 (holding that "incomplete" attorney advertising was not inherently misleading).

[375] *See Virginia State Board of Pharmacy*, 425 U.S. at 757.

[376] *See Pacific Gas & Electric Co.*, 475 U.S. at 9 (government cannot "force[] speakers to alter their speech to conform with an agenda they do not set"); *United Foods, Inc.*, 533 U.S. at 410 ("Just as the First Amendment may prevent the government from prohibiting speech, the Amendment may prevent the government from compelling individuals to express certain views.").

2. Professional Advertising

a. Current Regulatory Regime (Professional Advertising)

FDA imposes a number of requirements on advertising and promotional communications directed to health-care professionals that consist primarily of bans, disclosure requirements, or pre-approval and monitoring provisions.[377] Although most of these requirements apply equally to messages directed to professionals and those directed to consumers, Pfizer confines the analysis in this section to speech directed to professionals and treats DTC-specific issues in the following section.[378]

(i) Brief Summary; Fair Balance (Professional Advertising)

An ad or promotional communication for a particular product must be accompanied by a "true statement of information in brief summary relating to side effects, contraindications ... and effectiveness" of the product with respect to the use or uses that the message promotes.[379] FDA has construed the "brief summary" provision to require a manufacturer briefly to restate (although in not so brief a fashion) the information contained in the operative labeling

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[377] This category of recipients includes managed care entities and hospital formularies, as well as physicians.

[378] *See infra* Part III.E, at 155-65.

[379] 21 C.F.R. § 202.1(e)(1), (3), (4); *see also* 21 U.S.C. § 352(n). FDA exempts some advertisements from the brief summary requirements. These include reminder ads, which are used to call attention to the name of a product but which do not include any information about its indications or recommended dosage. 21 C.F.R. § 202.1(e)(2)(i). Reminder ads are not permitted for drugs that carry special warnings, called "black box" warnings, that have been imposed by FDA to highlight major issues with the product or for drugs that carry a rating of no higher than "possibly effective" in the Drug Efficacy Study. 21 C.F.R. § 202.1(e)(2)(i). The agency also deems advertisements that focus only on price to be reminder ads, and therefore exempt from the brief summary requirements, as long as they say nothing about the drug's safety or efficacy. In addition, FDA exempts "help-seeking" advertisements, which discuss certain diseases or health conditions and advise consumers to see their doctors for diagnosis and possible treatments. Statement of Dr. Nancy M. Ostrove, Deputy Director of DDMAC, before the Subcommittee on Consumer Affairs, Foreign Commerce and Tourism, July 24, 2001. Help-seeking advertisements are discussed in Part III.E, *infra* at pp. 155-65. Pfizer is not commenting on the extent to which the liberalization of these categories by the use of enforcement discretion could avoid First Amendment concerns. Pfizer has focused on the substance of ad modifications required rather than the mechanics of implementing them.

concerning the uses discussed in the particular communication.[380] The advertisements also may not "recommend or suggest any use that is not in the labeling accepted" for the drug.[381]

All advertisements and other promotional communications subject to this "brief summary" requirement must also provide fair balance, which is achieved when the risks of a product, including its side effects and contraindications, are generally with a prominence clearly identified compared to that of the benefits of the product.[382] FDA identifies twenty types of advertising communications that it considers to be per se "false, lacking in fair balance, or otherwise misleading,"[383] which would thereby render the subject drug misbranded under 21 U.S.C. § 352(n).[384] These include, *inter alia*, a comparison between two or more drugs made without "substantial evidence" – usually requiring additional head-to-head studies – to support it.[385] The agency imposes on manufacturers wishing to make such comparisons the burden of proving "that the advertisement is not, in fact, "false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the [FDCA]."[386]

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[380] 21 C.F.R. § 202.1(e)(4).

[381] *Id.* For a further discussion of off-label use promotion, *see* Section III. E, *infra*, at pp. 155-65.

[382] *Id.* § 202.1(e)(5).

[383] *Id.* § 202.1(e)(6).

[384] 21 U.S.C. § 352(n) (brief summary required to avoid misbranding); 21 C.F.R. § 202.1 (e)(5)(ii) (requiring fair balance in order to present "true statement of information in brief summary").

[385] *See* 21 C.F.R. § 202.1(e)(6) (prohibiting comparative ads without substantial evidence); FDA, Division of Drug Advertising, Policy statement on comparative promotional claims, Oct. 27, 1988 (defining "substantial evidence" as support for a comparison from at least two adequate and well-controlled studies involving the drugs at issue in head-to-head clinical trials). In 1997, Congress amended the FDCA to permit FDA to deem only "one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute "substantial evidence." FDAMA, Pub. L. No. 105-115 (codified at 21 U.S.C. § 355(d)); *see* H.R. Rep. No. 105-310, at 67.

[386] 21 C.F.R. § 202.1(e)(6).

In addition, FDA identifies thirteen additional types of advertising communications that it warns "may be false, lacking in fair balance, or otherwise misleading."[387] These include, *inter alia*, the failure "to provide adequate emphasis ... for the fact that two facing pages are part of the same advertisement when one page contains information relating to side effects and contraindications" and the failure "to include on each page or spread of an advertisement the information relating to side effects and contraindications or a prominent reference to its presence and location when it is presented as a distinct part of an advertisement."[388]

The agency also prohibits advertising that describes differences between a brand-name drug and its generic counterpart when the products are rated as therapeutically equivalent.[389]

(ii) Disclosure of Generic Name and Ingredients (Professional Advertising)

FDA requires that all prescription drug advertisements refer to the generic name of the drug.[390] The regulations specify where the generic name must be placed with respect to the trade name, demand that the generic identification be given a "prominence commensurate" with the trade name, and require that the generic name be printed in letters that are at least half as large as the letters used for the trade name.[391] FDA also requires all ads and promotional communications to provide the formula for the drug listing the ingredients in the same order as they appear on the label[392] and to "display the name of at least one specific dosage form."[393]

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[387] *Id.* § 202.1(e)(7).

[388] *Id.*

[389] *See* David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising,* 264 JAMA 2409, 2412 (1990).

[390] 21 U.S.C. § 352(n); 21 C.F.R. § 202.1(b)(1).

[391] 21 C.F.R. §§ 201.10(g)(1), 202.1(b)(1), (2).

[392] 21 U.S.C. § 352(n); 21 C.F.R. § 202.1(a)(2).

Any information in the advertisement "concerning the quantity of each such ingredient shall be the same as the corresponding information on the label of the product."[394] Ads may not use "a fanciful proprietary name for the drug or any ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition" that it does not.[395] Nor may ads "feature inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation."[396]

(iii) Submission and Pre-Approval (Professional Advertising)

In accordance with the FDCA, FDA does not require manufacturers to obtain prior approval for their advertisements "except in extraordinary circumstances."[397] Currently, the only "extraordinary circumstances" in which the agency requires prior approval are where:

- a drug sponsor or FDA "has received information that has not been widely publicized in medical literature that the use of the drug may cause fatalities or serious damage";
- FDA "has notified the sponsor that the information must be a part of the advertisements for the drug"; and
- [t]he sponsor has failed within a reasonable time ... to present to [FDA] a program ... for assuring that such information will be publicized promptly and adequately to the medical profession in subsequent advertisements" or has failed to comply with the program.[398]

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[393] 21 C.F.R. § 202.1(d)(2).

[394] *Id.* § 202.1(a)(2).

[395] *Id.* § 202.1(a)(3).

[396] *Id.* § 202.1(a)(4). Nor can ads use proprietary drug names that are confusingly similar to the proprietary or generic name of another drug. *Id.*

[397] *See* 21 U.S.C. § 352(n).

[398] *See* 21 C.F.R. § 202.1(j)(1).

The prior approval requirement persists until FDA deems that information regarding the dangers associated with the drug has been widely publicized in the medical literature and the agency notifies the sponsor that prior approval is no longer necessary.[399] Administrative hearing procedures are available to manufacturers who wish to challenge FDA's determination that preclearance is required for advertisements for a particular drug or FDA's determination that a particular advertisement is not approvable.[400]

Although FDA does not require prior approval in circumstances other than those outlined above, the agency nonetheless requires manufacturers to submit other types of advertisements and promotional communications at or before the time of initial dissemination or publication.[401] With respect to drugs approved under Subpart H of 21 C.F.R. § 314, entitled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses," FDA requires that the manufacturer submit – during the preclearance review period – ads intended to run during the first 120 days of marketing.[402] After such drugs are approved, FDA requires ads to be submitted at least 30 days prior to the intended time of initial dissemination of the advertisement.[403] FDA also typically reviews initial launch advertisements prior to their publication. Although this is not a requirement per se, FDA routinely requests that manufacturers submit these ads before running them.[404]

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[399] *Id.* § 201.1(j)(2).

[400] *Id.* § 202.1(j)(5).

[401] *Id.* § 314.81(b)(3).

[402] 21 U.S.C. § 314.550.

[403] *Id.*

[404] *See* 21 C.F.R. § 202.1(j)(4); FDA, Guidance to Expedite the Review of Launch Campaign Submissions, March 1994. Should a manufacturer not wish to comply with this request, FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) states that they should promptly notify DDMAC of this decision. *Id.* DDMAC

(iv) Types of Speech Subject to FDA's Advertising Requirements (Professional Advertising)

The requirements for advertisements and promotional communications listed above apply to messages in a variety of formats that are sponsored by drug manufacturers and directed to health-care professionals, including physicians, managed care entities, and hospital committees responsible for drug purchases.

Apart from more traditional means of communication – such as ads in published journals, magazines, newspapers, and promotional brochures and ads on cable channels directed toward health care professionals – FDA also considers certain other types of manufacturer speech to constitute advertising or promotional communications. For example, the agency treats exhibits sponsored by drug companies at medical meetings and all the materials displayed in such exhibits as advertising and/or promotional communications. These displays must meet the requirements listed above, as must company-supported CME programs that discuss the company's products.[405] In addition, FDA considers so-called "formulary kits" – which it has defined as "material prepared for review by pharmaceutics and therapeutics committees, etc., that discuss a regulated product and that are prepared for and disseminated to hospitals, managed health care organizations, buying groups, and other institutions" – as promotional communications subject to these regulations.[406]

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also states that any proposed safety or efficacy claims in initial ads should be cleared with the new drug division handling the application. *Id.*

[405] *See* Off-Label Information Dissemination, *infra*, for some additional provisions applicable to off-label information.

[406] *See* Wayne L. Pines, FDA Advertising and Promotion Manual ¶ 437 (Thompson Publishing Group 2000).

FDA treats all materials used by detailers in a similar fashion.[407] The manufacturer must authorize all information that its sales representatives distribute and must submit all material used by detailers to FDA for review at the time of initial dissemination.[408] Detailers may not alter such material in any way, even by underlining printed information.[409] FDA also regards detailers' oral statements about specific products as subject to the above regulations.[410]

In addition to materials provided to the medical community, FDA also considers materials that mention a specific drug product and are submitted by manufacturers to the press[411] or to the financial community[412] as promotional communications, and therefore subject to fair balance disclosures as well as all other requirements of the regulations governing advertising and promotional communications discussed above.

b. Current Enforcement Mechanisms (Professional Advertising)

FDA can enforce its regulation of promotional communications and advertisements through the means discussed above, including seizures, injunctions and criminal prosecution.[413] In practice, however, the agency often deals with them through administrative avenues; specifically, it sends out Notices of Violation or Warning Letters that inform the company of the

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[407] 21 C.F.R. § 202.1(l)(2) (labeling includes "detailing pieces").

[408] Wayne L. Pines, FDA Advertising and Promotion Manual ¶ 433 (Thompson Publishing Group 2000).

[409] *Id.*

[410] *Id.*

[411] *See* David G. Adams, FDA Regulation of Communications on Pharmaceutical Products, 24 Seton Hall L. Rev. 1399, 1401 (1994).

[412] FDA has developed policies to accommodate Securities and Exchange Commission mandates that publicly traded companies release to the investment community "material" information that can affect the value of company stock. These policies prohibit the release of detailed information about specific products unless FDA's requirements for promotional communications are met. *See, e.g.,* FDA, Warning Letter to The Upjohn Co. dated May 15, 1986. To the extent that these releases concern products in the pre-approval process, additional requirements apply.

[413] *See supra* Part III.A.2, at 67.

alleged violation, the actions that FDA wants the company to undertake to correct the violation, and the time frame in which this should occur. Typical corrective measures include requiring the manufacturer to (1) run corrective advertisements that the agency has approved word-for-word, (2) send out "Dear Healthcare Professional" letters to those who can be expected to prescribe the drug that was the subject of the offending ad, and (3) provide corrective instructions to sales representatives.[414]

c. Is the Restriction a Restraint on Protected Speech? (Professional Advertising)

FDA's advertising and promotional restrictions concerning communications to professionals about approved uses of prescription drugs consist of (1) bans, which forbid certain types of speech altogether; (2) submission and pre-approval provisions, which suppress speech for a period of time and may lead to outright prohibitions; and (3) mandatory disclosures, which compel manufacturers to convey certain messages that they otherwise might not choose to convey. As explained below, each of these types of restrictions operate directly to forbid or otherwise restrain certain types of speech for reasons that cannot be justified as incidental to conduct regulation. Accordingly, these restrictions are subject to the *Central Hudson* analysis.[415]

Protected Speech? Commercial speech about lawful activity that is truthful and not misleading is entitled to First Amendment protection.[416] In fact, the speech in advertisements and other promotional communications has been shown to have significant and cognizable value

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[414] 21 U.S.C. § 375; Arthur N. Levine, FDA Enforcement Manual ¶¶ 104, 500, 510 (Thompson Publishing Group 2000).

[415] *See supra* Part II.C.4, at 52-63 (discussing *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 566 (1980)).

[416] *Cent. Hudson*, 447 U.S. at 566.

for the recipients.[417] For example, comparative claims between brand-name drugs and their therapeutically equivalent generic alternatives – which FDA bans altogether – could have considerable value for the listener due to information that the speakers may have about dosage forms, formulations, or inert ingredients that the agency does not address in determining equivalency. Moreover, the fact that a promotional communication may offer less detailed information in comparison to the operative labeling does not render that communication necessarily untrue or misleading and therefore strip it of First Amendment protection.[418]

To the extent that other types of manufacturer speech are non-promotional in nature but nonetheless categorized by FDA as advertising, restrictions on that speech would be subject to strict scrutiny under the First Amendment. Material in this category could include communications to the media, such as press releases,[419] and releases to the financial community.[420] These messages do not necessarily "propose a commercial transaction" or

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[417] *See supra* Part I, at 1-18.

[418] *See supra* Part II.C.4.a, at 54.

[419] FDA's treatment of press releases and other communications to the media as promotional labeling is problematic. These communications cannot be deemed to serve the purpose of operative instructions for use – FDA's original conception of labeling – nor are they advertising, for these exchanges rarely, if ever, involve an explicit proposal of a commercial transaction, nor do they address the *Bolger* factors in all particulars. *See supra* Part II.C.4, at 52-53. At the very least, FDA may not impose a blanket policy of treating such communications as either labeling (operative instructions for use) subject only to *O'Brien* review or commercial speech subject only to the *Central Hudson* analysis. Rather, FDA must develop a more discriminating approach for determining what authority it may wield under various circumstances. As discussed in *supra* Part I.C.2, note 48, these communications may well involve constitutionally protected rights to respond to public controversies that warrant the application of full First Amendment safeguards.

[420] As with materials released to the media, FDA's policy on speech to the financial community appears flawed. It is not clear that releases to the investment community are commercial speech at all – or, if they are, that such releases are within FDA's regulatory jurisdiction beyond minimal safeguards concerning truthful and non-misleading accounts of the relevant drug reviews. These communications do not propose a commercial transaction concerning any named *drug*; if they serve a commercial purpose at all, it is to solicit purchase of the company's *stock*. Accordingly, courts could well deem FDA's power to impose disclosure obligations or other restrictions to be tightly constrained as this field is governed by the SEC, not FDA.

otherwise satisfy the *Bolger* analysis for commercial speech.[421] FDA should evaluate these materials on a case-by-case basis to characterize the speech correctly as either commercial or noncommercial.

Severity of Restraint: For the most part, FDA's regulations concerning advertisements and promotional communications consist of mandated messages rather than bans (*e.g.*, brief summary). As such, they do not suppress speech but rather compel manufacturers to engage in speech in which they might not otherwise choose to engage. Although this type of restraint as a cure for deception is constitutionally preferred to suppression in the commercial speech context, compelled disclosure requirements nonetheless raise serious First Amendment concerns and must be adequately justified under the governing level of scrutiny for the type of speech at issue.[422]

Moreover, some of FDA's professional advertising regulations suppress certain promotional communications altogether. These include FDA's twenty-item litany of promotional statements and other communications that it considers to be per se false, misleading, or lacking in fair balance. FDA's ban on ads containing comparative claims that are not based on substantial evidence (typically, but not always, two adequate and well-controlled clinical trials) and FDA's prohibition of ads comparing a brand-name drug with a therapeutically equivalent generic counterpart also function as complete bans on such speech. These regulations impose the severest form of restraint of all and must be scrutinized accordingly.[423]

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[421] *See*; *supra* Part II.C.4, at 52-53 (discussing *Bolger*, 463 U.S. at 66-67).

[422] *See United States v. United Foods, Inc.*, 533 U.S. 405, 410 (2001) ("Just as the First Amendment may prevent the government from prohibiting speech, the Amendment may prevent the government from compelling individuals to express certain views."); *supra* Part II.B, at 44-46.

[423] *See supra* Part II.B, at 44-46.

Several of FDA's regulations do not suppress speech altogether, but they do function as prior restraints. The most classic example is FDA's preclearance requirement on ads for particularly dangerous drugs whose dangers have not yet been widely disseminated.[424] FDA's requirement that manufacturers submit ads for accelerated approval drugs for serious or life-threatening illnesses 30-120 days before the ad runs also functions as a prior restraint even though FDA does not preclear these ads, and therefore manufacturers may run the ads as soon as the specified time period has expired barring a specific agency objection. FDA's request that manufacturers in the final stages of drug approval submit initial launch ads may have traits of a prior restraint as well, particularly given FDA's substantial leverage over manufacturers at this critical stage of product development. Under the general First Amendment presumption against prior restraints,[425] the agency's policy with regard to all of these ads should be closely scrutinized to determine both the necessity for such measures in light of the danger presented and their effect on the flow of information.[426]

To a certain extent, FDA seems cognizant of the need for care with its prior restraints on advertisements and promotional communications closely. The agency's regulations provide that the advance submission requirement for accelerated approval drug advertisements can be terminated when FDA determines that it is not necessary for the safe or effective use of the drug.[427] FDA will similarly terminate its prior approval requirement under 21 C.F.R. § 202.1(j)(1) for ads "[w]ithin a reasonable time after information concerning the possibility that

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[424] *See supra* Part III.D.2.a.iii, at 119-120.

[425] *See supra* Part II.B, at 41-42.

[426] *See supra* Part II.B, at 41-42. The general requirement that manufacturers submit promotional communications to FDA when they are first used does not function as a prior restraint – manufacturers are free to disseminate the communications without awaiting FDA's stamp of approval.

[427] 21 C.F.R. §§ 314.550, 314.560.

a drug may cause fatalities or serious damages has been widely publicized in medical literature.[428] To be in full compliance with the First Amendment, however, FDA should tread particularly carefully in this area and ensure that it can substantiate the extreme dangers which it relies upon to justify its prior restraints given the strong presumption against the constitutionality of such measures.[429]

Finally, FDA's warning that thirteen types of advertising communications "may" be false, misleading, or otherwise lacking in fair balance, while not forbidding such speech altogether, nevertheless may have a chilling effect on those communications by discouraging cautious manufacturers from engaging in such communications for fear of risking a dispute with the agency. The agency could dissipate this chilling effect, however, by instituting a hearing procedure in which the agency would be required to establish affirmatively that a particular ad in one of the thirteen questionable categories was false or misleading before it could require the manufacturer to discontinue the ad.[430]

Speech Restriction Incidental to Conduct Regulation? FDA's regulations of advertising and promotional communications target speech, not conduct. The agency could not "seriously contend[] that 'promotion' of an activity is conduct and not speech"[431] where, as here, "the activities at issue . . . are only 'conduct' to the extent that moving one's lips is 'conduct.'"[432] In fact, FDA's regulations operate directly to suppress some speech – such as comparative

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[428] *Id.* § 202.1(j)(2).

[429] *See supra* Part II.B, at 41-42.

[430] *See supra* Part II.C.4.a, at 56-59.

[431] *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 59 (D.D.C. 1998) ("*WLF*"), *extended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

[432] *Id.*

claims – whenever a manufacturer does not meet FDA's standard for making such speech, regardless of the objective truth of the claim. The agency also restrains advertising and promotional communications through its practice of mandating extensive disclosures in connection with such speech, such as the requirement that all ads contain a "brief summary" that, at least with respect to the print medium, is not at all "brief."

These speech restrictions, unlike those that apply to a drug's operative labeling, are not inherent components of FDA's gatekeeper regulations by which the agency primarily regulates manufacturer conduct to ensure safe and effective drug use. In contrast to operative labeling, professional advertising is designed to make doctors aware of a drug and its potential benefits; it is not intended to provide doctors with comprehensive use information, which doctors primarily and should obtain from the PDR or package inserts themselves.[433] Because, FDA's restraints on professional advertising and promotional communications primarily target the information flow from manufacturers to doctors they do not qualify for the more lenient *O'Brien* standard of First Amendment review accorded to incidental restraints on speech.[434]

Relevant Legal Standard: Most manufacturer speech subject to FDA's regulations in this area is properly categorized as commercial speech to the extent that the communication directly promotes the purchase of the product. For example, items such as print advertisements in medical journals promoting specific drugs, professional brochures serving the same purpose, or television advertisements about specific products on medical-themed cable channels are all intended to make doctors aware of the named drugs and their benefits in the hope that physicians

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[433] *See supra* note 252 and accompanying text.

[434] *See supra* Part II.C.3, at 51-52 (discussing *O'Brien*, 391 U.S. at 376).

will prescribe these pharmaceutical products when appropriate. Accordingly, FDA's regulation of these types of speech is subject to heightened scrutiny under *Central Hudson*.[435]

As discussed above, however, certain communications that the agency regulates as advertising or promotional communications may be fully protected under the First Amendment because they are scientific speech. Such protected speech could include press releases, financial disclosures, or responses to safety or efficacy issues raised by other interested parties. Since these communications constitute fully protected scientific speech, any applicable FDA restrictions would have to satisfy the highly rigorous strict scrutiny standard.[436]

d. What Substantial, Legitimate Interest Does the Restraint Serve? (Professional Advertising)

In determining the legitimate interests that FDA's regulation of professional advertising and promotional communications serve, it is useful to first consider interests that these restraints do *not* serve. Preservation of the agency's drug approval process and preventing unsafe or ineffective drugs from reaching the market cannot be deemed legitimate interests that are affected here because the speech at issue concerns uses for drugs that already have been approved as safe and effective.[437]

FDA could support certain professional advertising restrictions based on its unquestionably substantial interest in preventing false or misleading speech.[438] The agency cannot, however, justify categorical restrictions on the basis of this interest where it has no objective means or expertise for determining that promotional speech, as opposed to the

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[435] *See supra* Part II.C.4, at 52-63 (discussing *Cent. Hudson*, 447 U.S. at 566).

[436] *See supra* Part II.C.1, at 48-49.

[437] Off-label promotion is discussed in *infra* Section III.E, at 155-65.

[438] *See supra* Part II.A, at 19-39.

operative labeling, is false or misleading.[439] In this regard, FDA has misinterpreted the brief summary requirement and misapprehended the role of fair balance by placing more emphasis on balance than fairness. Pfizer does not take issue with the concept of "fair balance" to the extent that it requires an ad to be truthful and not to mislead. The company does, however, believe that it is constitutionally problematic for FDA to presume that its determination of the type of information appropriate for operative labeling (such as a detailed listing of all dangers, side-effects, and contraindications) necessarily sets the minimum standard for truthful, non-misleading assertions in advertising and promotional communications.[440] This is not to say that no disclosure mandates are permissible. However, the Constitution requires FDA to consider the context and purpose of the speech on a case-by-case basis in determining whether a particular promotional communication would be false or misleading absent certain disclosures.

The extremity of FDA's current approach is obvious when it is considered in the context of other advertised goods and services. For example, FDA's position on truth in advertising apparently would bar a rocking chair manufacturer from claiming that its product is the ultimate relaxer unless the manufacturer recited all caveats on the claim, down to possible discomfort of those with spinal injuries. These caveats also are true and certainly paint a more detailed picture of the nature of the claim, but the lack of the caveats does not render the assertion necessarily untrue or misleading to rocking chair consumers. Rather, the average consumer exposed to the ad is quite likely to understand that the phrase "the ultimate relaxer" has some implicit limitations.

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[439] *See supra* Part II.C.4.a, at 54.

[440] *See supra* Part II.C.4.a, 54 (discussing *Ibanez*, 512 U.S. at 143; *Zauderer*, 471 U.S. at 651).

In sum, FDA plays an important role in maintaining the integrity of the prescription drug marketplace by requiring manufacturers to be truthful in their promotional representations. The agency cannot, however, assert constitutional carte blanche to dictate what manufacturers may, must, and cannot say about their products in advertising merely based on FDA's own policy judgments of the types of speech that it believes to be more valuable than others or on FDA's determination of what appropriately should appear on a product's operative labeling to enhance the product's safe and effective use. Rather, FDA must affirmatively show that the promotional speech it regulates is otherwise false or misleading based on objective standards.

The substantiality of the agency's interest in maintaining the truthfulness of professional advertising would be strengthened if FDA could show that the false or misleading nature of a particular ad would cause doctors to engage in inappropriate prescribing practices that may harm consumers. However, FDA cannot merely assert such an interest in the absence of evidence that such harm is occurring. Courts are highly unlikely to accept the paternalistic notion that a trained physician should be presumed incapable of distinguishing between promotional communications and operative labeling. Rather, doctors should be presumed and encouraged to act responsibly and to refer to a drug's operative labeling as necessary when making prescribing decisions.[441] To overcome this presumption and establish the legitimacy of its regulations on the basis of this interest, the agency must be prepared to demonstrate affirmatively that a properly identified promotional communications, with more general disclosures, increase the risk that doctors will misprescribe the drug at issue.[442] Indeed, First Amendment considerations and sound public health policy dovetail in this regard, because FDA would be well advised to

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[441] *See supra* note 252 and accompanying text.

[442] *See supra* Part II.C.4.b, at 59-60.

reinforce the use of closely reviewed operative labeling as the only appropriate prescribing tool for physicians.

It is appropriate for FDA to be mindful that other forces also operate to support the agency's goal of ensuring that manufacturer speech concerning their products is truthful and not misleading. These include, but are not limited to, the pharmaceutical manufacturers' interest in maintaining their credibility in the medical community; the risk of product liability suits; the harms that adverse publicity could create in both political and financial circles; and the prospect of suits or enforcement actions under both false advertising laws.

Finally, the government has not identified a sufficiently substantial interest to support Congress's requirement that all prescription drug advertisements provide and prominently feature the generic name of the drug being advertised. The legislative history for that requirement indicates that the primary government interest behind this mandate was to "lend opportunities for ... competition to flourish" by giving physicians both the brand-name and the generic name of the drug so that they could choose to "prescribe the so-called generic equivalent by using the official name or by authorizing the pharmacist to select a product bearing the official name."[443] Promoting competition between products, however laudable a goal, is not the kind of interest that can support a government order compelling a private entity to speak against its will – particularly when such speech only benefits business competitors. As the Supreme Court concluded in *Pacific Gas & Electric Co. v. Public Utilities Commission of California*, the government cannot "force[] speakers to alter their speech to conform with an agenda they do not

[443] S. Rep. No. 87-1744, at 18 (1962).

set" or "penalize[] the expression of particular points of view" despite the speaker's "status as a regulated [entity]."[444]

e. Does the Restraint Directly Advance a Legitimate Interest? (Professional Advertising)

Assuming that FDA's interest in preventing inappropriate and potentially harmful prescribing practices as a result of false or misleading advertising is legitimate, the agency still must demonstrate that its restraints actually advance that interest in a direct and material way.[445]

As a general matter, it is questionable whether FDA's restraints on professional advertising directly advance FDA's interest: manufacturers of prescription drugs are not the only ones communicating information about these products, and unregulated third parties may thwart the agency's ability to control the information that professional audiences receive.[446] For example, manufacturers of non-prescription products are not subject to these same requirements, nor are pharmacy benefit management companies, independent researchers, citizen groups interested in a particular disease or condition, or even the government itself. Representatives of pharmacy benefit management companies and state insurance plans, commonly known as "counter-detailers," visit doctors to discuss individual doctor's prescribing practices and promote drugs that they believe doctors should prescribe instead of ones they currently use.[447] These

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[444] 475 U.S. 1, 9, 17 n.14 (1986). In the legislative history, Congress also obliquely alluded to one potential safety justification: that doctors might not be able to find the information necessary to prescribe a drug safely unless its generic name is included in all advertising. S. Rep. No. 87-1744, at 18 (1962) ("The use of the generic or official name is important so that practitioners and pharmacists can turn to the official compendia and other literature to ascertain the qualities and specifications of the product, and the competing product."). Because the PDR is indexed by both generic and brand names, however, this safety argument is not sustainable.

[445] *See supra* Part II.C.4.c, at 60.

[446] *See supra* Part I.C.2, at 12-14.

[447] *See* Marc Kaufman, *Doctors Hear Alternatives To Drug-Firm Sales Pitches*, Wash. Post, Aug. 5, 2002, at A01; Russell Gold, *States Battling High Drug Costs Appeal to Doctors to Help Fight*, Wall St. J., Aug. 22, 2001.

individuals have free rein to compare drugs and frequently highlight the benefits of generics versus brand names in particular. Yet FDA's rules forbid the manufacturers of the brand-name drugs – who are extremely knowledgeable about their products[448] – from responding in kind. Similarly, a patient advocacy group for diabetics could send out a newsletter promoting a prescription drug that its members may find valuable without any of the disclosures required by FDA, such as the brief summary, the generic name of the drug, or fair balance in presentation. The group's newsletter also may compare different drugs without basing this comparison on what FDA deems to constitute "substantial evidence." In short, the lively marketplace of ideas that now surrounds prescription drug products – with all the unregulated speakers involved – means that much of the agency's advertising regime cannot directly and materially advance many of the agency's specific objectives.[449]

The degree to which particular regulations directly advance FDA's interest depends on the nature of the regulation. For example, it is unclear whether many of the agency's mandatory disclosures (*e.g.*, brief summary) directly advance the agency's goal of preventing inappropriate prescribing practices. While mandating that every advertising and promotional communication for a drug be accompanied by a distilled version of the operative labeling and offset benefits with risks might conceivably check harmful prescribing practices, all of the relevant information already is available in the operative labeling itself. There is some indication that doctors already perceive the operative labeling as reprinted in the PDR, not promotional pieces, as the usual

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[448] *See Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 771 n.24 (1976) ("[O]rdinarily the advertiser seeks to disseminate information about a specific product or service that he himself provides and presumably knows more about than anyone else.").

[449] *See Greater New Orleans*, 527 U.S. at 193-94.

standard reference tool to use in making prescribing decisions for individual patients.[450] There is every reason to believe that this use would become virtually exclusive were FDA to make clear that all other communications served only a promotional, not an instructional, function. Moreover, because the PDR indexes all drugs not only by their generic name but by their brand name and manufacturer as well, FDA's generic name requirement is a duplicative tool, at best, for enabling doctors to learn more about a drug under consideration.[451] In short, FDA's disclosure requirements would not seem directly and materially to advance its interest in ensuring that drugs are administered safely and effectively.

By contrast, FDA's suppression of misleading advertising is constitutionally appropriate. For example, FDA's complete ban on twenty specific types of advertising communications, including comparative claims not based on substantial evidence, targets misleading speech with no commercial value. In eliminating the possibility of misleading speech through such bans, however, FDA must avoid overbreadth which would prevent doctors from receiving truthful and potentially valuable information, such as comparative information based on evidence that FDA does not recognize as "substantial" – including, rather ironically, truthful statements that correctly reflect the operative labeling that the agency already has approved for each of the drugs being compared.

FDA's submission and pre-approval provisions for professional advertisements likewise directly advance its interest in preventing false and misleading advertisements. For example, the

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[450] *See supra* note 252 and accompanying text. Pfizer understands that FDA itself is making strides to emphasize the critical importance of the operative labeling by making that labeling available over the Internet.

[451] Moreover, the generic name itself often is no more informative concerning the chemical structure and properties of a particular drug than the brand name. For example, the generic name for Cefobid is cefoperazone, while its chemical formula is 7-[(R)-2-(4-ethyl-2, 3-dioxo-1-piperazinecarboxamido)-2-(p-hydroxy-phenyl) acetamido-3- [(1-methyl-H-tetrazol-5-yl) thio] methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carbox-ylate. The generic name for Vioxx, rofecoxib, is similarly unrevealing about the structure of the drug: 4-[4-(methyl-sulfonyl)phenyl]3-phenyl-2(*5H*)-furanone.

agency's pre-approval requirement for ads for dangerous drugs in certain circumstances ensures that only ads involving high risk products that are truthful and nonmisleading will run since any unrestricted claim of benefit for such product would be misleading. FDA's thirty-day lead time in which to consider ads for accelerated approval drugs functions similarly; the time lag presumably enables FDA to object to promotional communications that it deems to be false or before they are run. To a lesser extent, FDA's *de facto* submission requirement for launch ads also directly advances FDA's interest in purging the drug marketplace of false or misleading ads by enabling FDA to monitor the types of ads manufacturers are running. Again, however, all of these restraints suppress valuable speech along with the harmful and their administration must be examined with a particularly scrutinizing eye.[452]

f. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Professional Advertising)

There are other, more narrowly tailored means of serving FDA's interest in preventing false and misleading ads. FDA's current policy of requiring all advertisements and promotional communications to contain mandatory disclosures concerning the side effects, contraindications, and the like that simply duplicate the detailed information set forth in the operative labeling is overbroad and fails to account for the useful role that advertising plays in the prescription drug marketplace. FDA does not have the constitutional authority to compel such an extensive amount of speech in advertisements – thereby forcing manufacturers to dilute the power of their messages with other messages – at least not until it can demonstrate that each disclosure is "reasonably related to the State's interest in preventing deception"[453] and that any legitimate

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[452] *See supra* Part II.B, at 41-42.

[453] *Zauderer*, 471 U.S. at 628.

concerns could not be addressed with less extensive compulsions to speak.[454] The constitutional protections accorded under *Central Hudson* require that FDA make a more exacting, evidence-based determination on a case-by-case basis of the need for particular disclosures with respect to an individual drug.[455] For much the same reasons, FDA's interpretation of fair balance also is overbroad to the extent that the agency construes it to require more than whatever disclosures are strictly necessary to render a particular ad truthful and non-misleading.

As a more narrowly tailored alternative, FDA could replace its extensive mandatory disclosures in promotional messages with a single required disclosure that explicitly identifies the material as promotional and directs physicians to "consult the operative labeling for more detailed and pertinent information concerning dosage, potential side effects, and contraindications."

FDA could also convert its mandatory disclosures into voluntary safe harbors, allowing manufacturers to choose whether to incorporate those disclosures into their promotional ads to physicians but guaranteeing manufacturers who do include such disclosures that they will not be subject to agency enforcement actions against assertedly false or misleading ads. FDA should delete altogether its generic name requirement because it does not directly advance any legitimate government interest.[456]

There are also more narrowly tailored alternatives to FDA's specific regulations prohibiting certain claims altogether. For example, instead of banning the twenty types of advertising communications that FDA considers to be per se false, misleading, or otherwise

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[454] *See supra* Part II.B, at 39-47.

[455] *See supra* Part II.C.4, at 44-46.

[456] *See supra* Part III.D.2.d, e, at 129-136.

lacking in fair balance, FDA could warn manufacturers that it will scrutinize such claims particularly closely and initiate enforcement actions against ads containing such claims if it believes that they are false or misleading, much as FDA now treats the thirteen additional types of claims that it states "may" be false, misleading, or otherwise lacking in fair balance. If the manufacturer has grounds to dispute FDA's charge concerning a particular claim, FDA then could be required to establish before an objective administrative body that the claim is, in fact, false or misleading, as Pfizer proposes above.[457]

FDA also could allow currently banned speech but require manufacturers to issue disclaimers or other disclosures to remove any potentially misleading impression that the ad might convey.[458] For example, the agency could allow comparative claims based on less than what FDA considers to be substantial evidence so long as the ads provide appropriate disclaimers notifying readers of the basis of the comparison and, when appropriate, the fact that FDA has neither approved nor endorsed the direct comparative assertions.[459] The agency likewise could allow comparisons between generics and brand-names with a disclaimer informing the audience that FDA has rated the drugs as pharmaceutically and therapeutically equivalent. The less-speech restrictive use of disclaimers accords with the teaching of the First Amendment that the agency, when addressing communications that are neither false nor "inherently" misleading,[460]

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[457] *See supra* Part II.C.4.a, at 54.

[458] *See Pearson*, 164 F.3d at 657-60 (requiring agency to consider use of disclaimers before banning speech altogether).

[459] It is not clear that the latter disclosure would be appropriate in all cases. For example, truthful comparisons based on the approved operative labeling for each drug would not appear to warrant an agency "non-review or endorsement" disclosure. Such comparative ads, when providing adequate disclosures, are unlikely to be false and misleading. Indeed, FDA's proposed changes to the labeling requirements for prescription drugs are designed to facilitate such comparisons. *See* Proposed Labeling Requirements, 65 Fed. Reg. at 81082.

[460] As stated in Section II.B, pp. 54-56, courts routinely reject regulators' assertions that speech is inherently misleading.

should first consider appropriate disclosures tailored to address likely points of confusion or misunderstanding.[461]

Non-speech regulatory alternatives may also be an option for successfully advancing FDA's public health and consumer protection objectives. The agency increasingly recognizes that a systematic risk management approach that harnesses the collective efforts of all parties involved in the drug development and health-care delivery system at various stages of the process may have a more profound effect in reducing drug risks than traditional commercial speech restraints.[462] By encouraging a greater information flow and degree of cooperation among industry stakeholders, the emerging risk-management approach appears more likely to combat the incidence of adverse drug events originating from inadequate information, lack of patient compliance with labeling instructions, and medical errors while also reducing the ostensible need for restrictions on commercial speech.

g. Recommended Rule and/or Policy Change (Professional Advertising)

With regard to mandatory disclosures, FDA could best bring its regulatory approach into compliance with First Amendment principles by adopting the recommendations suggested above. Specifically, the agency should replace categorical disclosure requirements with the simple directive that promotional material should be prominently labeled as such and should advise doctors to consult the operative labeling for complete information concerning the drug. This approach would reinforce the dichotomy between the two forms of information that FDA regulates and drive physicians to the source best suited to provide them with complete and

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[461] *See* Section II.C.4.a, at 44-46 (discussing, *inter alia*, *Peel*, 496 U.S. at 91, 110; *Ibanez*, 512 U.S. at 142, 145; *Zauderer*, 471 U.S. at 650-51); *see also Pearson*, 164 F.3d at 657-58.

[462] *See supra* Part II.A.4, at 35-39.

accurate information to ensure safe and effective administration of that product. The agency should also suspend enforcement of and encourage Congress to delete altogether the generic name requirement. Such a scheme would raise considerably fewer constitutional concerns, avoid much if not all of the need for case-by-case review, and serve to eliminate any confusion about the relative importance of operative labeling in promoting safe and effective drug usage. The First Amendment limits FDA's power to require disclosures in advertising beyond that actually required to address likely points of confusion or misunderstanding.[463]

At the same time, FDA could reshape its mandatory requirements (*e.g.*, brief summary) into optional "safe harbors" akin to those already in place for certain communications concerning off-label uses and guarantee to oppose any conflicting state law failure to warn claims on federal preemption grounds. This approach would allow the agency to shape what it deems to be best practices while also providing manufacturers the constitutional flexibility and incentive to run truthful and nonmisleading ads even though they may be outside of FDA's preferred ideal. It would also significantly reduce the number of advertisements outside the safe harbor constructs, thereby reducing the number of cases requiring individualized agency review. When devising such safe harbors, however, the agency must take care to craft them in a manner that is reasonably tied to the agency's interest in preventing false and misleading communications.

FDA could offer a similar safe harbor assurance to encourage voluntary prior review over certain types of advertising. Alternatively, the agency could require disclosures of the type discussed above – identifying the general cause for concern and stating that the products may have unknown risks except in the case of extremely high risk drugs where current policies seem appropriate.

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[463] See *supra* Part II.C.4.a, at 44-46 (discussing, *inter alia*, *Peel*, 496 U.S. at 91, 110; *Ibanez*, 512 U.S. at 142, 145; *Zauderer*, 471 U.S. at 650-51); *see also Pearson*, 164 F.3d at 657-58.

In addition, FDA should replace various prohibitions on commercial speech with disclaimers and other appropriate disclosures whenever possible, while still respecting the general constraints on the agency's power to compel speech. For example, ads making comparative claims could reveal the basis of the information used in the comparison, and ads comparing generics and brand names could include a disclosure advising that FDA has certified the drugs as equivalent. The agency also should make clear that manufacturers have a "right of response" on issues raised by third parties concerning the safety or efficacy of the manufacturer's product without regard to FDA's current fair balance requirements or other disclosures that otherwise might be necessary in advertisements.

The revised regulations outlined above would better respect manufacturers' First Amendment right to engage in truthful, non-misleading commercial speech that conveys messages of their choosing. These revisions undermine FDA's interest in supporting appropriate prescription practices among health-care professionals, which can, and should, be enforced primarily through comprehensive regulation of a drug's operative labeling.

3. DTC Advertising

The analysis in this section concerns FDA's power to regulate DTC advertising concerning approved uses of prescription drugs. As noted above, almost all of FDA's regulations of professional advertising apply equally to DTC advertising, although the latter is subject to additional regulations as well. To the extent that DTC and professional advertising regulations raise the same constitutional considerations, Pfizer does not repeat them here. Rather, Pfizer focuses on any analytical differences that may exist in the DTC context and on FDA's DTC-specific regulations.

This analysis is driven principally by one simple but profound point: because consumers are, by definition, shielded by learned intermediaries in the selection and use of prescription

drugs, it is not essential for DTC advertisements to outline to consumers what each and every particular risk of a drug might be. What is important is for DTC advertisements to alert consumers that such risks exist and that consumers should discuss them with their doctors. Doctors have complete and accurate information concerning the drug at issue from the operative labeling and can be presumed to act responsibly and with full information before issuing consumers a prescription. In light of the crucial safeguard provided by the knowledgeable professional who writes the prescription, FDA must be particularly careful not to restrict unduly a manufacturer's ability to communicate truthful, non-misleading information about its products. Pfizer discusses below how FDA should rethink certain DTC advertising regulations, many of which likely could not withstand a First Amendment challenge.

a. Current Regulatory Regime (DTC Advertising)

DTC advertising includes print and broadcast (*e.g.*, radio and television) advertisements, videotapes, cassettes, pamphlets, brochures, and other materials paid for by a drug company that are intended to be seen or used by a consumer and that mention a specific product directly or indirectly. With the exception of broadcast advertising, all DTC advertising must comply with the regulations applicable to professional drug advertising, such as the "brief summary"[464] and "fair balance" requirements.[465] Under this regime, manufacturers must, *inter alia*, summarize for consumers the prescribing information given to physicians – despite the fact that consumers are not trained to understand this information or able to obtain the products being promoted without their doctor's intervention. FDA does partially acknowledge the difference in professional and

[464] Reminder ads, which call attention to the name of a product without giving information on its indications or required dosages, and help-seeking ads, which discuss a disease and its symptoms rather than a specific product, do not have to comply with the brief summary requirement. *See* 21 C.F.R. § 202.1(e)(2)(i); Statement of Dr. Nancy M. Ostrove, Deputy Director of DDMAC, before the Subcommittee on Consumer Affairs, Foreign Commerce and Tourism, July 24, 2001.

[465] 21 U.S.C. § 352(n).

consumer audiences by encouraging print DTC ads to employ consumer-friendly language in the brief summary, but the advertisements still must contain all of the contraindications, warnings, major precautions, and all other frequently occurring side effects related to the advertised drugs.[466]

With respect to broadcast advertisements for consumers, FDA has modified the brief summary requirement in response to the difficulty of presenting the volume of information that this requirement entails in a meaningful way through media like television. Rather than provide the brief summary within the ad itself, DTC broadcast ads must instead (1) include a "major statement" of a product's critical risk information, (2) present indications, and contraindications in consumer-friendly language, and (3) make "adequate provision" for consumers to receive the full brief summary information from the manufacturer of the product being promoted.[467] The latter requirement involves significant effort on the part of the manufacturer, which must do all of the following:

- Establish a toll-free phone number where the full package label can be read to consumers over the phone or mailed to them;
- Instruct consumers to talk to their doctors for more information;
- Place the information in concurrently running print advertisements or publicly available brochures for those who do not want to contact the company or their doctors; *and*
- Place the information on the Internet at an address indicated in the advertisement.[468]

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[466] FDA, Draft Guidance for Industry, *Using FDA-Approved Patient Labeling in Consumer-Directed Print Advertisements* (2001), available at http://www.fda.gov/cber/gdlns/consumad.htm.

[467] FDA, Guidance for Industry, *Consumer-Directed Broadcast Advertisement* (Aug. 6, 1999), available at http://www.fda.gov/cder/guidance/1804fnl.htm.

[468] *Id.*

Unlike ads directed at professionals, FDA requests that DTC advertisements be submitted to the agency *before* they are run.[469] Although this, in theory, is a voluntary policy, it functions in practice as a mandatory requirement.[470] FDA's substantial enforcement authority functions to give the agency great *in terrorem* powers to ensure that even its "voluntary" policies are followed.

b. Current Enforcement Mechanisms (DTC Advertising)

Apart from FDA's substantial ability to enforce even allegedly voluntary policies, FDA has the same arsenal of enforcement weapons discussed above – *i.e.*, seizures, injunctions, criminal prosecution, and Notices of Violation or Warning Letters.[471]

c. Is the Restriction a Restraint on Protected Speech? (DTC Advertising)

Protected Speech? As true for professional advertising, commercial speech directed to consumers enjoys heightened First Amendment protection under *Central Hudson* so long as it concerns lawful activity and is not misleading.[472] The constitutionally protected status of such speech is consistent with empirical studies demonstrating that it is highly valued by patients and doctors.[473] DTC advertising educates patients about conditions and treatments of which they would not otherwise be aware and encourages them to seek help from their doctors for these

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[469] *See* 21 C.F.R. § 202.1(j)(4); FDA, Notice, Request for Comments, 61 Fed. Reg. 24,314, 24,315 (May 14, 1996).

[470] *See* 61 Fed. Reg. 24314 (recognizing that the DTC voluntary preclearance policy is "perceived [as a] requirement for manufacturers to obtain prior clearance from the agency for all prescription drug and biological DTC promotion").

[471] *See supra* Part III.B.2, at 67.

[472] *See supra* Part II.B, at 54.

[473] *See supra* Part I.B.1, at 4-6.

conditions.[474] In one study, a majority of physicians believed that DTC advertising has a positive impact on their interactions with their patients.[475] Further, studies have indicated that consumers who request drugs as a result of DTC ads are more likely to comply with their drug treatment regimes.[476]

Certain communications directed to consumers may deserve the highest degree of First Amendment protection. To the extent that speech aimed at consumers is scientific rather than commercial in nature – for example, communications discussing the symptoms of a disease that direct consumers to talk to their doctors for more information and do not mention any specific product – that speech would be accorded full protection under the First Amendment.[477]

Severity of Restraint: The severity of the DTC speech restrictions that apply equally to professional advertising are analyzed in that section.[478]

As for DTC-specific restraints, FDA's adequate provision requirement for broadcast DTC ads is, like other mandatory disclosure requirements, a less severe restriction on speech than an outright ban because it requires "more speech, not enforced silence."[479] The agency still must demonstrate, however, that the restriction passes muster under *Central Hudson*.[480]

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[474] Comments of the staff of the Bureau of Economics and the Bureau of Consumer Protection of the Federal Trade Commission, In Re: Direct-to-Consumer Promotion, January 11, 1961, at 13.

[475] Market Measures Interactive, DTC Dialogue: *Cholesterol & Mood/Anxiety Disorders,* 2001 (summarizing physician reports on over 400 office visits where patients initiated a discussion about a prescription drug).

[476] RxRemedy Information Services, *Impact of DTC Advertising Relative to Patient Compliance*, 2001.

[477] *See supra* Part III.D.2, at 48-49. FDA, in fact, considers these to be help-seeking ads and exempts them from certain mandatory disclosures. *See* Wayne L. Pines, *FDA Advertising and Promotion Manual* ¶ 415 (Thompson Publishing Group 2000).

[478] *See supra* Part III.D.2.c, at 123.

[479] *See supra* Part II.B, at 44-46 (discussing *Whitney*, 274 U.S. at 377).

[480] *See supra* Part II.C, at 52-53 (discussing *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 66-67 (1983)).

FDA's submission policy for DTC ads is not a restriction on speech. Even though manufacturers have treated FDA's request for DTC ad submissions as mandatory, FDA does not require manufacturers to delay running the ads until the agency has approved them.

Speech Restriction Incidental to Conduct Regulation? As Pfizer explained in the professional advertising section, FDA's advertising regulations directly target speech per se, not conduct, and therefore do not qualify for the more deferential *O'Brien* standard of review.[481]

Relevant Legal Standard: To the extent that manufacturer speech directed to consumers directly promotes the purchase of a specific product, the communication is properly categorized as commercial speech. For example, ads in consumer health magazines and commercials broadcast during primetime television that mention specific products and their uses clearly aim, *inter alia*, to make consumers aware of these products and encourage them to ask their doctors if the drugs might be right for them. Accordingly, this speech is entitled to protection under *Central Hudson*.[482]

To the extent that DTC advertisements do not promote a specific product, but rather act to educate consumers – *e.g.*, "help-seeking" advertisements, which simply inform consumers about particular conditions and encourage them to see their doctor for diagnosis and treatment, and "institutional" ads, which link a company to a field of research – such ads arguably are entitled to the highest degree of First Amendment protection.[483]

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[481] *See supra* Part III.D.2.c, at 127-28; *supra* Part II.C.3, at 51-52 (discussing *O'Brien*, 391 U.S. at 377).

[482] *See supra* Part II.C.4, at 52-63.

[483] FDA appears to recognize that this speech is entitled to additional protection in some contexts. For example, it properly does not apply all of its normal regulations to institutional ads and help-seeking ads but instead exempts them from the brief summary requirement. FDA, Direct-to-Consumer Promotion; Public Hearing, 60 Fed. Reg. 42851, 42852 (Aug. 16, 1995).

d. What Legitimate Interest Does the Restraint Serve? (DTC Advertising)

As with professional advertising, FDA's legitimate interest in regulating DTC advertising cannot be characterized as preserving the drug approval process or as keeping unsafe products off the market because the products being promoted here have already been approved for safety and efficacy and are available only with a doctor's prescription.[484] Similarly, FDA cannot assert a justifiable interest in prohibiting false or misleading speech per se absent an affirmative demonstration that the speech in fact is false or misleading.[485]

Nor could FDA claim that its DTC advertising regulations serve some legitimate fiscal interest of the government – by, for example, operating so as to reduce Medicare costs through onerous regulations that effectively suppress DTC ads and thereby suppress demand for advertised drugs. Advancing such a theory would require the agency to rely on notions that are constitutionally unsound. *Western States* already has made plain that the government may not assume that advertising audiences will act irrationally in response to truthful promotional speech.[486] Consequently, FDA would effectively be contending that keeping people ignorant of health-care treatments determined to be medically appropriate is a legitimate means of directly advancing the government's fiscal goals. That, in turn, would resurrect a serious issue under prong two of *Central Hudson*: to assert that the government has a "substantial" interest in

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[484] *See supra* Part III.D.2, at 129-33.

[485] *Id.*

[486] W. States, 122 S. Ct. at 1507-08 ("we have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information"). The Court also rejected the notion that physicians could not be relied upon "to refrain from prescribing compounded drugs to patients who do not need them in a world where advertising [is] permitted." *Id.*

restricting information flows in order limit effective treatment under Medicare would contradict the very foundation of the health-care program itself.[487]

FDA could, however, conceivably support other mandated disclosures in DTC advertising by asserting an interest in preventing drugs from being used in inappropriate ways. This interest would be based on an assumption that DTC advertising generates inappropriate consumer demand for drugs and that physicians improperly give in to such demands. FDA cannot assert, without proof, that excessive DTC advertising will cause doctors inappropriately to over-prescribe – the Supreme Court already has signaled in *Western States* that courts will dismiss such unsupported assumptions as disfavored paternalism.[488] In any event, relevant studies expressly contradict this assertion, reporting that doctors, in fact, are *not* unduly swayed by consumer demand to prescribe drugs unnecessarily or inappropriately.[489]

The substantiality of this interest is even more attenuated with respect to DTC advertising than with respect to professional advertising. Although consumers are the users of prescription drugs, they are not able to obtain these products without a prescription from a licensed medical practitioner. FDA has recognized that the crucial information exchange point is the doctor, who, as the "learned intermediary," is responsible for educating himself or herself concerning a drug's benefits and risks, conveying that information to his or her patients, and ensuring patient

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[487] Furthermore, it is not at all clear that government cost containment is a cognizable interest under Central Hudson; there appears to be no precedential support indicating that such an interest would be sufficiently substantial to burden protected speech. Yet even if it were, the argument would founder on the last prong of Central Hudson, for there are many other non-speech-suppressive alternatives that would more directly serve the interest, e.g., readjusting Medicare eligibility and compensation formulas.

[488] *See Thompson v. W. States Med. Ctr.*, 122 S. Ct. 1497, 1507-08 (2002).

[489] *See, e.g.*, Market Measures/Cozint, *Doctors Say Direct-to-Consumer Advertising of Rx Medicines Improves Physician/Patient Relationship* (Feb. 14, 2002) (study based on over 400 office visits reports that "almost 70 percent of physicians do not feel pressure to prescribe medication requested by patients who saw a DTC advertisement").

compliance.[490] Doctors therefore act as a check on any information that consumers may receive that would cause them to be misled into asking for a prescription drug inappropriately.[491]

FDA might also assert an interest in regulating DTC ads to prevent consumers who already possess prescription drugs from using them inappropriately. It is conceivable that FDA might fear that a DTC ad for a product a consumer is currently taking that emphasizes the relative safety of the drug could cause the consumer to dismiss or delay reporting any harmful side effects he or she develops from the drug.

Such fears, however, are premised on the paternalistic notion that consumers will use truthful information irrationally, a disfavored assumption under the commercial speech doctrine.[492] FDA's own research demonstrates that consumers understand that the purpose of DTC advertising is to make them aware of therapeutic products and the conditions they treat so that they can engage in meaningful health care dialogue with their physicians; it is not to diagnose conditions or to provide comprehensive instructions for use and warnings concerning a

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[490] U.S. Dep't of Health and Human Svcs., FDA, "Managing the Risks from Medical Product Use – Creating a Risk Management Framework: Report to the FDA's Commissioner From the Task Force on Risk Management," May 1999, at 76.

[491] With respect to FDA's requirement that DTC ads include the generic name of the advertised drug, the government's asserted interests do not appear sufficiently substantial to justify the mandate even with respect to professional advertising. *See supra* Part II.C.4, at 52-63 (discussing *Cent. Hudson*, 447 U.S. at 566). There is even less justification for generic name mandates in DTC advertising because the information is meaningless to the intended audience.

[492] *See supra* Part II.B, at 42-44. Compare FTC actions specifically rejecting proposed rules that would have required advertising for over-the-counter drugs to mirror FDA labeling content. *See* FTC, *Advertising for Over-the-Counter Drugs*, 46 Fed. Reg. 24,584 (proposed May 2, 1984) (to be codified at 16 C.F.R. pt. 450); FTC, *Advertising for Over-the-Counter Antacids*, 49 Fed. Reg. 46,156 (proposed Nov. 23, 1984) (to be codified at 16 C.F.R. pt. 451).

prescription drug.[493] That research also shows that consumers will not be induced by truthful advertising to ignore their physicians' instructions, advice, and prescribed course of treatment.[494]

Particularly in light of the foregoing considerations, FDA cannot simply presume that the harm that the regulations seek to prevent is actually occurring. Rather, the *Central Hudson* test squarely places on the agency the burden of showing "that the harms it recites are real"[495] to demonstrate that its interests are sufficiently substantial to support its restrictions on consumer advertising. In particular, the agency may not rely on its current approach for determining whether consumers might be misled by particular DTC ads that do not comport with all of FDA's requirements.[496] As compared with professional advertising, FDA has even less claim to expertise in determining how consumers would interpret particular claims in DTC advertising. Even the federal agency with the most experience with consumer perceptions about advertising, the Federal Trade Commission, often relies on outside experts or surveys to determine how claims are understood by consumers.[497] FDA must rely upon similar empirical data to substantiate its conclusions that a particular DTC ad is misleading and should afford manufacturers an objective administrative process for contesting any such determinations, as described in Part II.C.4.a., *supra*.

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[493] Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, *Assessments of Physician and Patient Attitudes toward DTC Advertising of Prescription Drugs* (2002), *available at* http://www.fda.gov/cder/ddmac/dtcindex.htm.

[494] *Id.* Question 39 of FDA's research report reveals that 70% or more of surveyed patients disagree with this statement: "Advertisements for prescription drugs make it seem like a doctor is not needed to decide if a drug's right for me," *available* at: http://www.fda.gov.cder/ddmac/Itcindex.html.

[495] *Edenfield v. Fane,* 507 U.S. 761, 770-71 (1993); *supra* Part II.B, at 59-60.

[496] *See Pearson v. Shalala*, 164 F.3d 650, 659-61 (D.C. Cir. 1999).

[497] *See* "Deception Policy Statement", Letter from the Federal Trade Commission to the Honorable John Dingell, Chairman, House Energy and Commerce Committee (Oct. 14, 1983), *reprinted as appendix to Cliffdale Assocs.*, 103 F.T.C. 110, 176 (1984).

FDA nonetheless may be able to support reasonable regulations – such as a modified version of its adequate provision mandate – that require manufacturers to point consumers to a means of obtaining additional information about an advertised drug as one permissible way to guard against misleading ads. The purpose of DTC advertising, after all, is to alert interested consumers to particular prescription drugs so that they can find out more about them, and unlike doctors, consumers typically do not have a product's operative labeling at their fingertips. Thus, FDA may well be justified in requiring manufacturers in both print and broadcast to advise interested consumers of a readily accessible way to learn more about the product to enhance their understanding and to assist them in engaging their doctors in informed conversations about the drug.

Finally, in evaluating the substantiality of FDA's interests in regulating DTC advertising, the agency must also weigh the First Amendment's countervailing interest in protecting the flow of useful commercial information. As discussed in detail above, DTC advertising has significant value for consumers, and the First Amendment safeguards their right to receive it.[498]

e. Does the Restraint Directly Advance a Legitimate Interest? (DTC Advertising)

Assuming that FDA's interests in preventing consumer misuse of drugs and physician misprescription of drugs arising from false or misleading DTC ads are substantial, it is still questionable whether FDA's regulations of these advertisements directly advance these interests. As was true with the agency's regulation of professional advertising, many unregulated messages reach the intended audience for DTC advertisements, which belies any claim that regulating only

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[498] *See supra* Part I.B, at 3-10; *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 757 (1976); *Pacific Gas & Elec. Co*, 475 U.S. at 8.

one type of speaker will remove the risk of harm arising from inappropriate consumer reliance on misleading messages.[499]

Even more to the point, FDA already acknowledges that it has other, non-speech-restrictive means of ensuring that consumers use prescription drugs safety: the presence of learned intermediaries in the process. This safeguard includes not just doctors but pharmacists; FDA has testified to Congress that pharmacists are a "crucial safety link" in the drug distribution chain, providing risk and benefit information to consumers.[500] These additional checks against consumer misuse of prescription drugs may render many of FDA's regulations of DTC advertising largely superfluous.

With respect to FDA's specific policies and regulations, and in particular FDA's speech bans and its submission and pre-approval provisions, the analysis provided in the professional advertising section largely applies in the DTC context as well.[501]

With respect to FDA's mandatory disclosure requirements for DTC ads in particular, the degree to which they directly advance the agency's legitimate interests is questionable. Arguably, the brief summary or major statement and adequate provision requirements might prevent consumers from (1) being confused about the identity of a drug or how to use it or (2) requesting a drug that they do not need from their doctors. On the other hand, there is evidence in FDA's prescription drug labeling rulemaking that suggests that the mandated

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[499] *See supra* Parts I.C, at 10-17, III.D.2.d, at 129-33.

[500] Statement by Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, Before the Committee on Health, Education, Labor and Pensions, U.S. Senate, Feb. 1, 2000.

[501] *See supra* Part III.D.2.e, at 133-36.

disclosures actually thwart FDA's interest in promoting clear, understandable consumer ads that deter drug misuse.[502]

The detailed and often highly technical information required for DTC print ads effectively replicates large portions of the operating labeling – communications that are designed to serve the needs of the physicians who prescribe the drug, not the laypersons who receive them. Requiring the inclusion of information written for medical professionals may serve no real purpose other than to confuse consumers or even distract their attention from a few key warnings that may be warranted to avoid deception. Worse, replication of operative labeling in DTC ads may mislead consumers into believing that they have full operational knowledge concerning a particular product and cause them to treat lightly, or even disregard, a doctor's instructions concerning usage of the drug. Some consumers might even resort to irresponsible physicians supporting Internet dispensers without medical examinations. Still, FDA may better advance its interests with a provision requiring manufacturers to provide consumers with at least one means of access to the operative labeling which is reasonably calculated to prevent self-help consumers from being misled by arguably incomplete ads.

f. Could More Narrowly Tailored Alternatives Serve the Same Interest? (DTC Advertising)

There are numerous more narrowly tailored means of serving FDA's interest in restraining false and misleading DTC ads from either which could induce consumers to misuse drugs or inappropriately request and receive prescription drugs. These largely track the alternatives suggested in the professional advertising section above and include the conversion of prior restraints and speech bans into optional safe harbors, the conversion of speech bans into a

[502] *See* 65 Fed. Reg. at 81,083. FDA found that its existing "format and content requirements ... have contributed to an increase in the amount, detail, and complexity of labeling information. This has made it harder for health care practitioners to find specific information and to discern the most critical information in product labeling." *Id.*

warning list of potentially problematic speech for industry guidance only, the deletion of the generic name requirement, and the replacement of extensive mandatory disclosures with targeted disclaimers.[503]

For DTC ads, the suggested disclaimer could simply state that the advertised drug is available only by prescription, that all prescription drugs carry risks, and that consumers should consult their doctors for more information. FDA also may be able to sustain some minimal but reasonable mandate that manufacturers provide consumers access to additional information about the advertised product – including even its operative labeling – by, for example, posting that data on the drug company's website and providing consumers with the URL. The use of this disclaimer and information referral in place of extensive mandated disclosures would better delineate the relative roles of doctor and patient in the prescription drug arena. The agency should not attempt to duplicate the doctor's communicative role through compelled speech in DTC ads that cannot realistically achieve the desired effect.

g. Recommended Rule and/or Policy Change (DTC Advertising)

FDA's regulations for DTC advertisements should reflect some basic realities relevant to the constitutional considerations at issue here. Consumers cannot obtain the prescription drugs being promoted without the intervention of a physician, and it is this physician – not ads – upon whom consumers should, and do, rely for fundamental drug safety and usage instructions. Pfizer recommends that FDA revise its approach to DTC advertising by adopting the narrowly tailored measures outlined immediately above. This regime would properly reinforce the primary role of the doctor in educating consumers about particular products and would harmonize FDA's DTC advertising regulations with First Amendment constraints.

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[503] *See supra* Part II.D.2.f, at 136-39.

E. ADVERTISING AND OTHER SPEECH CONCERNING UNAPPROVED USES OF APPROVED PRESCRIPTION DRUGS ("OFF-LABEL USE")

In this section, Pfizer addresses First Amendment limitations on FDA's power to regulate communications from manufacturers to physicians and consumers that refer or relate to unapproved uses of prescription drugs being lawfully shipped for approved uses. FDA believes that because each new use of a drug requires an independent New Drug Approval, a manufacturer's shipment of that drug with the intent that it be sold for unapproved uses violates the basic prohibition of 21 U.S.C. § 355 and also potentially renders all shipments of the drug misbranded because they lack adequate instructions for the unapproved, but intended, use.[504] Thus, FDA views speech that demonstrates a manufacturer's intent to create a market for that use as unprotected by the First Amendment or otherwise subject to restriction under *Pittsburgh Press*[505] and *Wisconsin v. Mitchell.*[506]

On the other hand, FDA recognizes that it has no power to control the practice of medicine: physicians are free to use approved drugs for off-label purposes. Off-label use, often generated by the cost and delay of the FDA review process, is not only widespread but also reflects the "state of the art" in critical care areas like oncology.[507] Moreover, off-label use differs from the use of chemical and biological entities never approved by FDA because drugs used off-label have passed FDA safety review both in healthy subjects (phase II) and in populations manifesting on-label indications. Thus, the public health issues affecting off-label

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[504] 65 Fed. Reg. 14,286 (March 16, 2000) ("off label use" guidance); *see also* Brief for the Appellants at 6-7, *Wash. Legal Found. v. Henney,* 202 F.3d 331 (D.C. Cir. 2000) (No. 99-5304).

[505] *Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations,* 413 U.S. 376, 388-89 (1973).

[506] 508 U.S. 476, 489 (1993).

[507] *Wash. Legal Found. v. Friedman,* 13 F. Supp. 2d 51, 56 (D.D.C. 1998) ("WLF"), *extended sub nom. Wash. Legal Found. v. Henney,* 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part on other grounds,* 202 F.3d 331 (D.C. Cir. 2000).

use are largely issues of efficacy.[508] Moreover, in Section 401 of the 1997 FDAMA (as reauthorized in 2002), Congress recognized that there is public health value in manufacturer circulation of certain third-party materials concerning off-label uses and has created – in FDA's view – a "safe harbor" for that circulation.[509]

Pfizer believes that FDA properly can seek to safeguard the fundamental prior approval regulatory regime by foreclosing the active promotion of off-label uses by manufacturers. On the other hand, given the reality of off-label uses, the multiple sources of information concerning those uses, and the substantial value to physicians and consumers of information concerning those uses, Pfizer believes that FDA must refine its existing guidelines to broaden and clarify permitted non-promotional dissemination of off-label information.

1. Current Regulatory Regime (Off-Label Speech)

FDA flatly forbids a manufacturer from "recommend[ing] or suggest[ing] any use that is not in the labeling accepted" in any of its promotional materials.[510] FDA extends this prohibition to manufacturer exhibits at medical meetings,[511] discussions at manufacturer-supported CME programs,[512] and manufacturer communications with formulary committees and other buyer

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[508] FDA has attempted to address any potential safety issues in its pending rulemaking on revised professional labeling. *See* Proposed Labeling Requirements, 65 Fed. Reg. at 81,082.

[509] 21 U.S.C. §§ 360aaa *et seq.*; Brief for the Appellants at 34-35, *Wash. Legal Found. v. Henney,* 202 F.3d 331 (D.C. Cir. 2000) (No. 99-5304).

[510] 21 C.F.R. § 202.1(3)(4).

[511] Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56,412, 56,413 (Nov. 27, 1992) ("CME Draft Policy"), finalized in the Final Guidance on Industry Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (Dec. 3, 1997) ("CME Final Guidance").

[512] *Id.* at 56,412.

organizations.[513] In addition, FDA's general restriction on false and misleading communications referring to any approved drug applies to off-label information.[514]

FDA must permit circulation of certain "enduring materials" under the FDAMA Section 401 safe harbor created by Congress.[515] In addition, FDA recognizes that other circulations of enduring materials may be permissible so long as they do not manifest the intent to promote off-label use,[516] but FDA has not precisely spelled out how this line is to be drawn. Similarly, FDA has provided "safe-harbor" guidance on the question of whether Continuing Medical Education ("CME") meetings are sufficiently independent to avoid attributing off-label use information flows to manufacturers, but the agency has not drawn a bright line between independent and manufacturer-sponsored meetings.[517] Finally, FDA has not sought to interfere with manufacturer responses to physician-initiated inquiries on off-label use or other communications it deems to be exclusively of scientific interest.[518] FDA provides no other definitive guidance on off label promotion.

2. Current Enforcement Mechanisms (Off-Label Speech)

Given its legal position, FDA can use the full panoply of generally available legal remedies including seizures, injunctions and criminal prosecution to enforce its prohibitions on

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[513] 21 C.F.R. § 314.81(b)(3); 62 Fed. Reg. 64,074, 64,078 (Dec. 3, 1997).

[514] 21 C.F.R. § 99.101 (a)(4).

[515] 21 U.S.C. §§ 360aaa *et seq.*

[516] 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996) ("Reprint Guidance").

[517] 62 Fed. Reg. 64,074 (Dec. 3, 1997).

[518] 21 U.S.C. § 360aaa – 6(a); 21 C.F.R. § 99.1(b); *see also* 21 C.F.R. §312.7 (scientific interaction exchanges concerning investigational new drugs.)

circulating off-label information.[519] In addition, where a manufacturer agrees with FDA to circulate materials within a FDAMA Section 401 safe harbor and subsequently breaches that agreement, FDA may seek sanctions and injunctive relief under FDCA Section 310(z).

3. Is the Restriction a Restraint on Protected Speech? (Off-Label Speech)

There is no doubt that FDA's existing regime substantially limits manufacturers' ability to circulate information regarding off-label uses of their products. How much of that information is subject to constitutional protection is a nuanced issue.

Protected Speech? Just as FDA reviews manufacturer statements with respect to unapproved substances to determine whether they manifest the requisite intent to invoke FDA jurisdiction over shipment and labeling, FDA might argue that its off-label restrictions simply create benchmarks for characterizing shipping and labeling. FDA would thus argue that its determinations of intended off-label use do not regulate speech at all but properly consider speech to characterize conduct.[520] FDA also might argue that any limitation imposed on speech which shows the intent to promote off-label use is indirect and properly incidental to its main purpose of regulating shipping and instructions for use.[521]

FDA has contended that manufacturer communications on off-label use are "inherently misleading" because FDA has not approved their content. That contention, however, has been resoundingly rejected by the courts[522] and now appears untenable. Nevertheless, FDA does have

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[519] *See supra* Part III.A.2, at 67.

[520] *Wisconsin v. Mitchell,* 508 U.S. 476, 484, 486, 489 (1993); *Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations,* 413 U.S. 376, 388-89 (1973).

[521] *United States v. O'Brien*, 391 U.S. 367, 376-77 (1968).

[522] *WLF*, 13 F. Supp. 2d at 66-69; *Pearson v. Shalala*, 164 F.3d 650, 655 (1998).

a legitimate interest in insuring that such communications do not improperly lay claim to government approval.[523]

Where manufacturer statements do not establish an intent to claim unapproved uses, FDA restrictions clearly restrain protected speech. The Supreme Court's decision in *Western States*, together with the lower court decisions in *Pearson* and *WLF* have removed all doubt as to whether speech concerning FDA-regulated products merits constitutional protection. Thus, First Amendment limitations must be recognized in any effort to regulate the dissemination of off-label information as opposed to unlawful shipments. This is particularly true where the circulations expressly disclaim both FDA approval and manufacturer endorsement of the use discussed.[524]

Severity of Restraint: The FDAMA Section 401 safe harbor requires both preclearance of manufacturer enduring material circulations by FDA and the supplementation of those materials with materials designated by FDA. The safe harbor thus has the hallmarks of a classic prior restraint and would be highly suspect if used as a mandatory standard.[525] FDA, however, has clearly stated that manufacturers need not conform to Section 401 limitations to engage in lawful circulations and thus has attempted to remove Section 401 as an operative prior restraint.[526]

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[523] *WLF*, 13 F. Supp. 2d at 66-69.

[524] For example, a manufacturer might circulate materials for the information of the professional community with a disclaimer stating that: [Manufacturer] provides this information to promote scientific disclosure and exchange. [Manufacturer] does not recommend this use and has not established [drug] to be safe and effective for this use. FDA has not determined this use to be safe and effective.

[525] *See supra* Part II.B, at 41-42.

[526] *See* 65 Fed. Reg. at 14,287 ("If a manufacturer does not proceed under section 401, that failure does not constitute an independent violation of the law.").

Speech Restriction Incidental to Conduct Regulation? The FDCA forecloses the shipment of new drugs unless FDA has found them to be safe and effective for each of their intended uses. FDA might, therefore, argue that any limitation imposed on speech that shows the intent to promote off-label use is indirect and properly incidental to its main purpose of regulating shipping and instructions for use.[527]

Relevant Legal Standard: The vast majority of the material at issue under this rubric is generated by third parties for scientific purposes. FDA does not restrict it in its original form – which raises a significant question as to the appropriate First Amendment standard that should apply to any further dissemination of this material by manufacturers. Under current FDA restraints, such communications plainly cannot propose a commercial transaction without running afoul of the limitation on off-label promotion. Given this explicit restraint, there are substantial reasons to doubt that these communications warrant anything less that the "strict scrutiny" protection accorded to scientific speech.[528] The only bases for according it any lesser First Amendment protection is the mere identity of the re-circulator and the potential commercial benefit that might flow from physicians' decisions to use the drug. These are slim reeds, together or apart, upon which to classify the speech as commercial.[529] The better approach is to

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[527] *See supra* Part II.C.3, at 51-52 (discussing *O'Brien*, 391 U.S. at 376-77).

[528] *See Keyishian v. Bd. of Regents*, 385 U.S. 589, 603 (1967) ("[Academic] freedom is therefore a special concern of the First Amendment . . . ."); *WLF*, 13 F. Supp. 2d at 62. ("Scientific and academic speech reside at the core of the First Amendment."); *Bd. of Trs. of Leland Stanford Junior Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ("It is equally settled, however, though less commonly the subject of litigation, that the First Amendment protects scientific expression and debate just as it protects political and artistic expression.").

[529] *See Bellotti*, 435 U.S. at 784 (observing that First Amendment does not support "the proposition that speech that otherwise would be within the protection of the First Amendment loses that protection simply because its source is a corporation"); *accord Greater New Orleans Broad. Ass'n, v. United States*, 527 U.S. 173, 191 (1999) ("Government presents no convincing reason for pegging its speech ban to the identity of the owners or operators of the advertised casinos."); *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 488-89 (1995) ("There is little chance that [regulation] can directly and materially advance its aim, while other provisions . . . directly undermine and counteract its effects."); *Pac. Gas & Elec. Co.*, 475 U.S. at 912 ("[W]e have held that speech does not lose its protection because of the corporate identity of the speakers."); *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 580

allow its scientific content, rather than its source, to determine its constitutional classification,[530] including cases in which the substantive scientific information accrues from manufacturer-sponsored or manufacturer-conducted research.

Four years ago, the U.S. District Court for the District of Columbia (Lamberth, J.), in reviewing a challenge raised by the Washington Legal Foundation to FDA's restrictions on circulation of third-party enduring materials, held that such circulation could be considered commercial speech rather than scientific speech.[531] Pfizer believes that conclusion, never reviewed by the appellate court, is incorrect. Nevertheless, the combination of FDA's strong interest in arresting false and misleading statements about drug products, together with the agency's own recognition of the distinction between promotional and informational circulations, suggests that the level of First Amendment protection accorded here may not affect the outcome of the analysis.

4. What Substantial, Legitimate Interest Does the Restraint Serve? (Off-Label Speech)

Congress has determined that the public health is best protected by foreclosing the shipment of new drugs unless FDA has found them to be safe and effective for each of their intended uses.[532] As the Supreme Court recently recognized in *Western States*, "[p]reserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible

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(1980) ("[T]he economic motivation of a speaker [should not] qualify his constitutional protection.") (Stevens, J., and Brennan, J., concurring in judgment); *supra* Part II.B, at 41.

[530] *N.Y. Times Co. v. Sullivan*, 376 U.S. 254 (1964).

[531] *WLF*, 13 F. Supp. 2d at 64.

[532] *See supra* Part II.A.3, at 19-39.

to be subject to that approval process."[533] Moreover, FDA has a substantial interest in ensuring "that off-label uses of previously approved drugs are subjected to the FDA's evaluation process."[534] This prior approval requirement serves both to prevent the shipment and use of unsafe and ineffective drugs and to enhance testing and package insert disclosures through the approval process.[535] If manufacturers could evade pre-approval by establishing a narrow use and then actively promoting one or more unscreened additional uses, it could erode the FDA's 1962 Act prior approval authority.

FDA also might assert that its restraints on off-label speech serves the public health by limiting actual unsafe and ineffective use. That argument would be harder to sustain given the prior safety approval of drugs used off-label and the widespread empirical evidence – not contested by FDA – that off-label uses can be highly beneficial. Nevertheless, some off-label uses may not be effective and, in any event, are not supported by the rigorous instructions for use required for approved uses. To the extent that off-label information is, in fact, false or misleading, FDA advances a legitimate public health interest in restraining it to prevent improper prescribing.

5. Does the Restraint Directly Advance FDA's Legitimate Interest? (Off-Label Speech)

FDA's restraints on overt promotion directly advance FDA's interest in safeguarding the integrity of the prior approval regime and encouraging supplemental applications for on-label use. If manufacturers could openly promote off-label uses, even with disclaimers advising of the lack of FDA approval, the underlying regime would be called into question and the public could

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[533] *Thompson v. W. States Med. Cent.*, 122 S. Ct. 1497, 1505 (2002).

[534] *WLF*, 13 F. Supp. 2d at 71.

[535] *Id.*

be deprived of the confidence generated by FDA review of drug products and their instructions for use.

It would be considerably more difficult for FDA to show that suppressing non-promotional information relating to off-label use that is not demonstrably false or misleading would directly advance the government's interest in safe and effective drug use. In a world of diverse drug information sources and Internet dissemination, it is at least unclear whether suppressing manufacturer dissemination would restrict or modify actual off-label use. To the contrary, it is arguable that manufacturer circulations that clearly disclaim FDA approval can actually enhance safe and effective use – because (1) the agency can monitor such communications for false or misleading information, and (2) manufacturers are likely to include warnings on unsafe uses for product liability purposes. Thus, suppression of overtly promotional manufacturer claims through the *in terrorem* effect of vague guidances does not directly advance FDA's legitimate interests.

6. Could More Narrowly Tailored Alternatives Serve the Same Interest? (Off-Label Speech)

FDA's legitimate interest in bringing additional drug uses on-label could be served by decreasing the cost and delay involved in processing supplemental applications and by increasing the benefits to manufacturers arising from the approval of such applications. Pioneer manufacturers now may hesitate to expend the resources necessary to meet FDA's exacting approval standards because possible additional uses serve only small populations or because generic manufacturers may "free ride" on pioneer expenditures through mandatory or formulary substitution. Although the general reforms necessary to limit cost and delay are beyond the scope of these comments, FDA and Congress could otherwise act to increase the benefit of supplemental approvals, as described below.

First, FDA could take regulatory action to reform the Orange Book so that A/B equivalency is not accorded to generic drugs that are not approved for uses granted by supplemental application. Existing law provides a three-year exclusivity period to a manufacturer gaining a new use approval, but that exclusivity is effectively defeated by rating generics that disclaim those uses as A/B equivalents and permitting them to be substituted off-label for the supposedly exclusive pioneer. By giving substance to the congressional grant of exclusivity, FDA could incentivize additional on-label use without any speech restriction at all.

Second, Congress could grant additional incentives for new on-label uses for all populations similar to those granted in FDAMA for pediatric uses. Historically, pediatric off-label use has been very significant and of great concern to interest groups who believed that on-label testing and labeling would benefit pediatric populations. In the 1997 FDAMA and 2002 BPCA, Congress responded to those concerns by granting additional incentives for on-label initiatives.[536] Incentives, rather than speech suppression are a constitutionally preferred method of encouraging on-label use.[537]

Because these two more narrow – and non-speech-infringing – alternatives would advance the government's interest in fostering supplemental applications, the result would be that any remaining promotion of off-label uses likely would warrant greater enforcement scrutiny. FDA's restrictions thus would more narrowly target those manufacturers seeking to evade the agency's safety and efficacy review because the uses cannot be scientifically substantiated. Given the strength of FDA's interest in preserving the integrity of the FDCA,

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[536] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997); Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002).

[537] *WLF*, 13 F. Supp. 2d at 73 (The existence of "adequate incentives . . . to get off-label treatments on- label is central to this court's finding that the First Amendment is violated by the Guidance Documents.").

Pfizer believes that a narrower prohibition on overt promotion of off-label uses would be consistent with the First Amendment values.

Pfizer does not believe, however, that the vague, *in terrorem* prohibitions in FDA's existing guidance on the dissemination of off-label information can withstand constitutional scrutiny. There may be circumstances where the flow of information from the manufacturer, taken together with other conduct, establishes a covert endorsement notwithstanding the absence of any overt promotional statements. In those selected instances, or in cases where the information circulated is false or misleading, FDA should reserve the right to take improper shipment or misbranding enforcement action. In all other cases, however, Pfizer believes that the First Amendment constrains FDA from taking action against the dissemination of off-label information accompanied by disclosures which make clear that: (a) FDA has not approved the use discussed; (b) the manufacturer is not recommending or prescribing the use discussed; and (c) the information is provided for the information of, and to promote dialogue with, the prescribing community, which must make its own determination with respect to the use discussed. Given those narrowly tailored disclosures, Pfizer believes that the value of bringing non-misleading off-label information to physicians significantly outweighs any government interest advanced by its suppression.

7. Recommended Rule and/or Policy Change (Off-Label Speech)

Pfizer does not believe that FDA's labeling rules regarding off-label use require modification. Those rules properly address and foreclose overt promotion of off-label uses, with apparent government sanction. Pfizer does believe, however, that FDA's existing guidance on informational circulations should be withdrawn and replaced with the simplified guidance set forth in the immediately preceding subsection.

IV. CONCLUSION

Pfizer appreciates this opportunity to comment on First Amendment issues raised by FDA's Request. Pfizer looks forward to further participating, through its reply comments, in the useful and timely discussion that FDA's Request has initiated and to an appropriate response from FDA. Pfizer firmly believes that timely FDA action to recognize First Amendment interests and to harmonize them with health and safety concerns will have substantial long-term benefits for the administration of the FDCA and the public health. To that end, Pfizer suggests that once FDA has had the opportunity to assimilate the comments and reply comments filed in this proceeding, it immediately revoke its guidances that are inconsistent with the First Amendment principles as demonstrated by Pfizer's and others' comments and issue new guidances more in keeping with those principles. Pfizer further suggests that FDA issue revised proposed regulations and publish them in the Federal Register for public comment in a Notice of Proposed Rulemaking.

Respectfully submitted,

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By: 

George W. Evans
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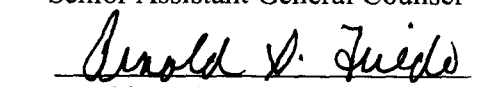

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Index: Section(s) of Comments Responsive to FDA's Specific Questions in 67 Fed. Reg. 34942 (May 16, 2002)	
Questions	**Responsive Sections**
1. Are there arguments for regulating speech about drugs more comprehensively than, for example, about dietary supplements? What must an administrative record contain to sustain such a position? In particular, could FDA sustain a position that certain promotional speech about drugs is inherently misleading, unless it complies with FDA requirements? Does anything turn on whether the speech is made to learned intermediaries or to consumers? What is the evidentiary basis of such a distinction?	I.C (pp. 10-17); II.C.4. (pp. 52-63); III.C.3-7 (pp. 97-107); III.D.2-3 (pp. 116-154); III.E.3 (pp. 158-161)
2. Is FDA's current position regarding direct-to-consumer and other advertisements consistent with empirical research on the effects of those advertisements, as well as with relevant legal authority? What are the positive and negative effects, if any, of industry's promotion of prescription drugs, biologics, and/or devices? Does the current regulatory approach and its implementation by industry lead to over-prescription of drugs? Do they increase physician visits or patient compliance with medication regimes? Do they cause patient visits that lead to treatment for under-diagnosed diseases? Does FDA's current approach and its implementation by industry lead to adequate treatment for under-diagnosed diseases? Do they lead to adequate patient understanding of the potential risks associated with use of drugs? Does FDA's current approach and its implementation by industry create any impediments to the ability of doctors to give optimal medical advice or prescribe optimal treatment?	I.B.1 (pp. 4-6); 1.C.3 (pp. 14-17); III.D (pp. 107-154)
3. May FDA distinguish claims concerning conventional foods from those relating to dietary supplements, taking into account limits on claims that can be made about foods in the Nutrition Labeling and Education Act, 21 U.S.C. 301, 321, 337, 343, 371? What must an administrative record contain to sustain or deny	N/A

claims on food labels? How can information best be presented in a succinct but non-misleading fashion? To what extent do assertions in claims need qualifications or disclaimers added to the label to avoid any misconceptions that consumers may draw? Is there a basis to believe that consumers approach claims about conventional foods and dietary supplements differently?	
4. Should disclaimers be required to be in the same (or smaller or larger) size of type and given equal prominence with claims? Is there any relevant authority or social science research on this issue?	III.B.2 (pp. 80-86); III.D.2.c-g (pp. 123-141); III.D.3.c-g (pp. 144-154)
5. How can warnings be made most effective in preventing harm while minimizing the chances of consumer confusion or inattention? Is there any evidence as to which types of warnings consumers follow or disregard?	III.D.3.c-g (pp. 144-154)
6. What arguments or social science evidence, if any, can be used to support distinguishing between claims made in advertisements and those made on labels? Does the First Amendment and the relevant social science evidence afford the Government greater latitude over labels?	II.A.1-3 (pp. 19-35); II.B (pp. 39-47); II.C.2-4 (pp. 49-63); III.B.1.c-g (pp. 76-79); III.B.2.c-g (pp. 82-86); III.B.3.c-g (pp. 89-94); III.D (pp. 107-154); III.E (pp. 155-165)
7. Would permitting speech by manufacturer, distributor, and marketer about off-label uses undermine the act's requirement that new uses must be approved by the FDA? If so, how? If not, why not? What is the extent of FDA's ability to regulate speech concerning off-label uses?	III.E (pp. 155-165)
8. Do FDA's speech-related regulations advance the public health concerns they are designed to address? Are there other alternative approaches that FDA could pursue to accomplish those objectives with fewer restrictions on speech?	II.A (pp. 19-39); III.A.5-7 (p. 70); III.B.1.e-g (pp. 78-79); III.B.2.e-g (pp. 84-86); III.B.3.e-g (pp. 90-94); III.C.5-7 (pp. 104-107); III.D.2.e-g (pp. 133-141); III.D.3.e-g (pp. 151-154); III.E.5-7 (pp. 162-165)
9. Are there any regulations, guidance, policies,	III.A.6-7 (p. 70);

and practices FDA should change, in light of governing First Amendment authority?	III.B.1.f-g (p. 79); III.B.2.f-g (pp. 85-86); III.B.3.f-g (pp. 91-94); III.C.6-7 (pp. 104-107); III.D.2.f-g (pp. 136-141); III.D.3.f-g (pp. 153-154); III.E.6-7 (pp. 163-165)